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ACUTE MOUNTAIN SICKNESS -

PREDICTION AND TREATMENT DURING CLIMBING EXPEDITIONS

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ACADEMIC DISSERTATION

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HEIKKI KARINEN

ABSTRACT

Acute mountain sickness (AMS) is a common problem while ascending at high altitude. AMS may progress rapidly with fatal results if the acclimatization process fails or symptoms are neglected and the ascent continues. It affects 25% of those ascending to altitudes of 1850 to 2750 m, 42% at altitudes of 3000 m, and even 84% of those attempting a tourist flight to Lhasa, Tibet (3860 m). The most common reason for altitude illness is a too rapid ascent. There is a need for a non-invasive, specific, and convenient field method for the detection of inadequate acclimatization and impending AMS. Arterial oxygen saturation (SpO_2) measurement is useful in anticipating AMS, but it is susceptible to many disruptive factors in the field (for example temperature). Autonomic cardiac response to increasing altitude could be a low-cost non-invasive test to predict impending AMS, in addition to helping distinguish those who are at risk for AMS and those who are acclimatizing well.

The purpose of the present study was to: 1. assess the prevalence of the symptoms and signs of acute mountain sickness among Finnish travelers climbing Mount Kilimanjaro, Tanzania; 2. investigate if post-exercise oxygen saturation (Ex-SpO2) at high altitudes predicts AMS better than arterial O_2 saturation at rest (R-SpO_2) or resting heart rate (HR) alone; 3. evaluate if heart rate variation (HRV) level or HRV changes have a relationship to AMS during ascent and provide new information on the deterioration of cardiac autonomic function as measured by HRV, not only at altitudes between 2400 and 5000 m, which are most frequent among climbers, but also at extreme altitudes above 5000 m in field conditions; 4. generate tools for AMS for non-medical persons to estimate the risk in field conditions; and 5. describe a typical AMS case and the difficulties to treat AMS at field conditions. The data was collected during several treks to Kilimanjaro and climbing expeditions to Denali, Shisha Pangma, Ulugh Muztagh, Island Peak, and Mount Everest 2001-2009.

The incidence of AMS was very high (75%) for the trekkers at Mt Kilimanjaro. In climbing expeditions, subjects susceptible to AMS had lower SpO_2 at rest and especially during exercise before the clinical manifestations of AMS so daily measurements of SpO_2 were taken at these times to best predict the subsequent AMS at higher altitude if ascending continued. Subjects susceptible to AMS had lower root mean square successive differences and high-frequency power of HRV before the clinical manifestations of AMS than those who acclimatized well and did not get AMS 2-5 days later if ascending continued.

The treatment of AMS in the field is difficult and time consuming, where possibilities for medical treatment and oxygen substitution might be limited. Prevention is the safest and the most efficient method of care. Realising the risk of mountain sickness, active inquiry about symptoms and correctly timed reaction to them, in other words interrupting the ascent or descending, helps to reduce, and even to prevent, the development of serious problems.

TIIVISTELMÄ

Vuoristotauti (AMS) on yleinen ongelma, kun noustaan yli 2500 m korkeuteen. AMS voi edetä nopeasti henkeä uhkaavaksi, jos sopeutuminen vallitsevaan korkeuteen epäonnistuu tai oireet ovat jääneet huomioimatta ja nousu jatkuu. Sairastuvuus on n. 25 % 1850–2750 m korkeudessa ja 42 % 3000 m korkeudessa. Lhasaan (3860 m), Tiibetiin lentäen matkustavista jopa 84 % sairastuu. Tavallisin syy AMS:n on liian nopea nousu. Vuoristotaudin diagnoosi on oireperusteinen ja tarve ei-kajoaviin, kenttäoloissakin toimiviin mittausmenetelmiin taudin tunnistamiseksi ja ennakoimiseksi on ilmeinen. Veren happisaturaation (SpO_2) mittaus auttaa AMS:n ennakoimisessa mutta se on altis monille häiriötekijöille (esim. lämpötila). Autonomisen hermoston sydänvasteiden kuten sydämen sykevaihtelun (HRV) muutosten on arveltu olevan edullinen ei-kajoava menetelmä ennakoida AMS.

Tämän tutkimuksen tavoitteena oli 1. arvioida AMS:n esiintyvyyttä suomalaisilla matkailijoilla Kilimanjarolla; 2. selvittää onko rasituksen jälkeinen SpO_2 parempi ennustamaan kehittyvää AMS:a kuin lepo SpO_2 tai leposyke (HR) yksinään; 3. tutkia HRV:n ja AMS:n välistä yhteyttä ja tuottaa uutta tietoa HRV muutoksista tavanomaisten kiipeilykorkeuksien (2400–5000 m) lisäksi äärimmäisissä korkeuksissa (> 5000 m); 4. tuottaa AMS riskin arviointiin työkaluja myös maallikoiden käyttöön sekä 5. kuvata tyypillinen AMS potilastapaus sekä sen hoitoa kenttäolosuhteissa. Tutkimusaineisto koottiin kyselytutkimuksena Kilimanjarolla sekä kenttämittauksin Denali, Shisha Pangma, Ulugh Muztagh, Island Peak ja Mount Everest retkikuntien aikana 2001–2009.

Tutkimuksen perusteella AMS:n esiintyvyys suomalaismatkailijoilla Kilimanjarolla oli erittäin korkea (75 %). Ylävuoristokiipeilyretkikunnissa AMS:lle alttiiden kiipeilijöiden lepo- ja erityisesti rasituksen jälkeinen SpO_2 laski merkittävästi ennen AMS:n kliinisten oireiden ilmaantumista. Samoin HRV:n RMSSD ja HF komponenttien lasku 2400 m korkeudessa ennakoi AMS:n kehittymistä ylempänä 2-5 vuorokautta myöhemmin, mikäli nousua jatkettiin ilman lepopäiviä.

Vuoristotaudin hoito kenttäolosuhteissa on vaikeaa ja aikaa vievää. Ennaltaehkäisy on turvallisin ja tehokkain menetelmä AMS:n hoidossa sillä lääkehoidon mahdollisuudet ovat rajalliset ja olosuhteista riippuen potilaan evakuoiminen alas voi olla mahdotonta. Päivittäiset lepo- ja rasitus-SpO_2 sekä HRV mittaukset voivat auttaa erottamaan hyvin sopeutuvat kiipeilijät niistä, joille myöhemmin voi tulla AMS korkeammalla. Vuoristotaudin riskin tiedostaminen, oireiden aktiivinen seuraaminen ja oikea-aikainen reagointi niihin, eli nousun keskeyttäminen tai laskeutuminen, voi estää myöhempien vakavien ja henkeä uhkaavien ongelmien kehittymisen.

CONTENT

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Karinen H, Peltonen J, Tikkanen H.
Prevalence of acute mountain sickness among Finnish trekkers on Mount Kilimanjaro, Tanzania: an observational study.
High Altitude Medicine & Biology 2008; 4:301-306

II Karinen H, Peltonen J, Kähönen M, Tikkanen H.
Prediction of acute mountain sickness by monitoring arterial oxygen saturation during ascent.
High Altitude Medicine & Biology 2010; 4:325-332

III Karinen HM, Uusitalo A, Vähä-Ypyä H, Kähönen M, Peltonen JE, Stein PK, Viik J, Tikkanen HO.
Heart rate variability changes at 2400 m altitude predicts acute mountain sickness on further ascent at 3000-4300 m altitudes.
Frontiers in physiology 2012; 3:1-7 DOI:10.3389/fphys.2012.00336.

IV Karinen H, Tikkanen H.
Two AMS cases and their treatment at field. Case report.
International Journal of Occupational Medicine and Environmental Health 2012; 25(3):1–6 DOI 10.2478/S13382-012-0037-3

The publications are referred to in the text by their roman numerals. The original publications have been reproduced with the permission of the copyright holders.

ABBREVIATIONS

AMS	Acute mountain sickness
A-a DO_2	Alveolar-to-arterial PO_2 difference
CaO_2	Arterial oxygen content
SpO_2	Arterial oxygen saturation
R-SpO_2	Arterial oxygen saturation at rest
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
HR	Heart rate
HRV	Heart rate variability
HACE	High altitude cerebral oedema
HAPE	High altitude pulmonary oedema
HF	High frequency
HVR	Hypoxic ventilatory response
SD1	Instantaneous short-term (beat-to-beat) variability
LLS	Lake Louise Score
SD2	Long-term continuous variability of all RR -intervals
LF	Low frequency
$\dot{V}O_2max$	Maximal oxygen uptake
Δ SpO_2	the difference between R-SpO_2 and Ex-SpO_2
Mean RR (NN)-interval	mean interval between normal QRS-complexes
O_2	Oxygen
$PaCO_2$	Partial pressure of carbon dioxide of the artery blood
PO_2	Partial pressure of O_2
Ex-SpO_2	Post exercise SpO_2
SD	Standard deviation
SDNN	Standard deviation of the NN intervals
RRI	The lengths of successive normal RR intervals
RMSSD	The Square root of the mean squared differences of NN-intervals
TINN	The triangular interpolation of NN interval histogram
VLF	Very low frequency
WHO	World Health Organization

REVIEW OF THE LITERATURE

1. INTRODUCTION

According to the World Health Organization (WHO) statistics, around 140 million people live permanently at altitudes higher than 2500 m (WHO 1996). The number of lowland dwellers travelling to altitude for work (soldiers, miners, construction workers, and astronomers), for seeking adventure or recreation (skiing, trekking, and climbing) at high altitudes has greatly increased in recent decades. Acute altitude illnesses are potentially serious conditions that can affect otherwise healthy and fit individuals who ascend too rapidly to altitude. They include high altitude headache (HAH), acute mountain sickness (AMS), high altitude cerebral oedema (HACE), high altitude pulmonary oedema (HAPE) (Imray et al. 2011), high altitude cough syndrome (Khumbu cough) (Litch and Tuggy 1998), high altitude retinopathy (Butler et al. 1992), and transient neurological disorder at high altitude (Cauchy et al. 2002) or high altitude global amnesia (Litch and Bishop 1999, Litch and Bishop 2000).

Health care practitioners may be involved in expeditions themselves, but the awareness of potential altitude related problems is important even for healthcare practitioners working at lower altitude, as patients may ask for advice regarding the safety of a proposed journey and how to prevent illness at altitude (Imray et al. 2011). The most important of the acute altitude illnesses are AMS, HAPE, and HACE.

The ascent to the altitude requires adaptation and acclimatisation to both lower air pressure and diminished partial pressure of oxygen (Hackett and Roach 2001). If the adaptation process fails due to too rapid an ascent rate or to the exceptional characteristics of the climber, one or more altitude related illnesses may result. AMS is the most common of these problems.

If those at risk of AMS could be detected more efficiently than is currently possible, prophylactic medicine like acetazolamide could be used, or the ascent rate of the whole expedition could be optimized to avoid the risk of changing the climbing expedition into a rescue mission.

2. ALTITUDE RELATED ILLNESSES

2.1. DEFINITION OF HIGH ALTITUDE

High altitudes can be defined as following (Imray et al. 2011):

- Intermediate Altitude 1500-2500 m
- High Altitude: 2500-3500 m
- Very High Altitude: 3500-5500 (5800) m
- Extreme Altitude: above 5500 (5800) m
- "Death Zone": above 8000 m

Each of these has different associations with physiological changes. At intermediate altitude the first signs of physiological changes are detectable. Arterial oxygen saturation may be above 90% and altitude illnesses are rare but possible with rapid ascent, exercise, and susceptible individuals. Altitude illness is common at high altitude when individuals ascend rapidly, and it is more common at very high altitude. Arterial oxygen saturation may be below 90% and marked hypoxemia occurs during exercise. The highest permanently inhabited town in the world at the present time appears to be La Rinconada, a mining village of over 7000 people in southern Peru at an altitude of up to 5100 m (West 2002). Subjects present marked hypoxemia at rest at these extreme altitudes. There is progressive deterioration, despite maximal acclimatisation, and permanent survival is not thought to be possible (Imray et al. 2011). The term "death zone" was originally coined in a book published in 1952, "The Mountain World" by Swiss doctor Edouard Wyss-Dunant, and this point is generally tagged as 8000 m where the atmospheric pressure is less than 356 millibars (Darack 2001). Before the entering the "Death zone", prolonged acclimatisation (> 6 weeks) is essential. Most mountaineers require supplementary oxygen to climb safely. Arterial oxygen saturations may vary from 48 to 55% (measurement done by Finnish Everest expedition at the summit of Mt Everest 2009). Rapid deterioration is inevitable and time spent above this altitude is strictly limited. (Imray et al. 2011).

2.2. NORMAL ACCLIMATIZATION

Acclimatization is the process by which the body adapts to the decreased availability of oxygen at high altitudes and adequate acclimatisation is essential for safe travelling in the mountains. It includes a number of physiological changes that occur over a variable time course (Figure 1). The most important are respiratory and

haematological changes (Moore et al. 1998). Some changes take place within minutes while others take several weeks. At intermediate to high altitudes, a significant degree of acclimatisation takes place over two to four days, but the adjustment process can take more days or even weeks depending on the altitude.

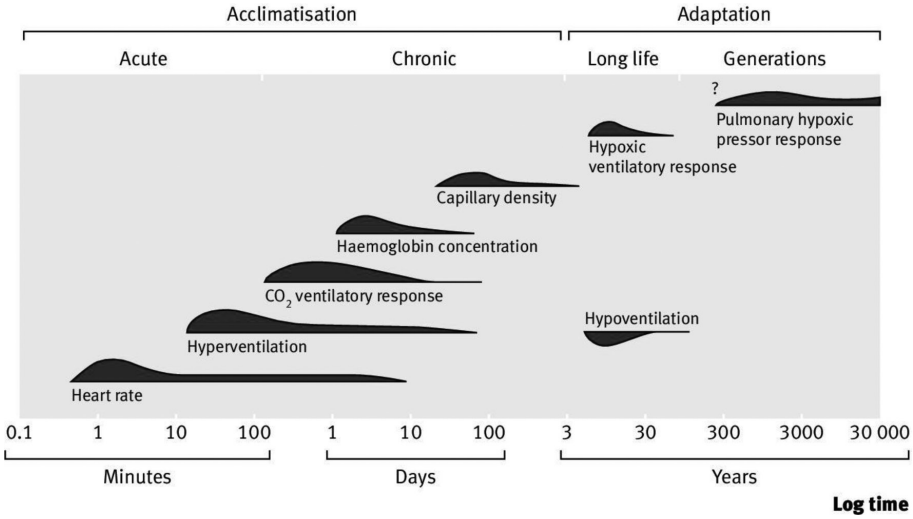


Figure 1. Time course of physiological adaptations to altitude. Time course of acclimatisation and adaptive changes plotted on log time scale. The curve of each response denotes the rate of change. (Adapted from Imray et al. 2011, originally Peacock 1998).

Ventilation rapidly increases with acute hypoxic exposure, and this hypoxic ventilatory response (HVR) was evident even after 56 or 62 days (Steinacker et al. 1996, Savourey et al. 1996) of chronic exposure from a Himalayan expedition. An enhanced HVR is generally presumed to enable better performance at altitude by maintaining arterial oxygen saturation levels (Schoene et al. 1984, Masuyama et al. 1986). Another common adaptation with chronic hypoxic exposure is an elevation in erythropoiesis and total haemoglobin mass (Pugh 1964), enabling greater oxygen delivery to the body for a given cardiac output (Gunga et al. 2007). Normal acclimatization also includes the rise of the sympathetic activity of the muscles (Mazzeo et al. 1995), increased urine excretion, changes in breathing rhythm during sleeping (Cheyne-Stokes – type breathing), nightly wakings and the change of sleep to abstract and strange, and subject may have dyspnoea (Ward et al. 1995**).** Cerebral artery dilatation due to hypoxia maintains cerebral oxygenation at extreme altitude and in acute hypoxia and this supposed to cause headache (Wilson et al. 2011). The decreased partial pressure of oxygen (PO_2) starts acclimatization and, as a consequence, the RR increases to improve the PO_2. At the same time, the

partial pressure of arterial carbon dioxide ($PaCO_2$) becomes smaller. This respiratory alkalosis will usually be balanced within an hour with urine excretion and bicarbonate secretion (Rodway et al. 2003), which takes place in the kidneys and has increased over the first 24–48 hours at altitude. The exact reason for the increase in urine excretion is unknown, but is believed to be important for acclimatization when the electrolyte balance changes when ascending high altitude (Basnyat and Murdoch 2003, Cumbo et al. 2002). This is why ascent to altitude often results in dehydration, also owing to exercise, hyperventilation, and limited access to water. It is important to drink plenty of fluids during acclimatization so that the sufficient diuresis will be maintained (Barry and Pollard 2003). Dehydration leads to the decrease in urine excretion and increased risk to experience acute mountain sickness. In published case studies, weakening diuresis and ketosis have been connected to serious AMS. Patients have been dehydrated due to an inadequate fluid intake and diuresis has not started leading to fluid accumulation in the tissues (for example Bärtsch et al.1991, Karinen and Tikkanen 2005). Although an association between AMS and dehydration has been noted (Basnyat et al. 2001), it is unclear whether dehydration is an independent risk factor for AMS. Acclimatization to the new altitude begins immediately but the symptoms of mountain sickness will usually develop in a 6–12 hour window after arriving at the new altitude. Development of serious mountain sickness usually takes 12–48 hours, but some serious anticipating symptoms can also be evident earlier (Hackett and Roach 2001, Basnyat and Murdoch 2003). If an ascent rate to the new altitude is fast, and the compensation mechanisms weakened, symptoms can begin even within an hour (Hackett and Roach 2001). The rate of acclimatisation varies between individuals and takes at least 2 days without symptoms after the arrival to the new altitude (Barry and Pollard 2003). The most important risk factors for the development of high-altitude illness are rate of ascent, altitude reached (especially the sleeping altitude), and individual susceptibility (Basnyat and Murdoch 2003).

2.3. ALTITUDE ILLNESSES

Altitude related illnesses can be both acute and chronic (Rupert and Koehle 2006). Acute altitude related illnesses includes high altitude headache (HAH), acute mountain sickness (AMS), high altitude cerebral oedema (HACE), high altitude pulmonary oedema (HAPE) (Imray et al. 2011), high altitude cough syndrome (Khumbu cough) (Litch and Tuggy 1998), high altitude retinopathy (Butler et al. 1992), and transient neurological disorder at high altitude (Cauchy et al. 2002) or high altitude global amnesia (Litch and Bishop 1999, Litch and Bishop 2000).

Subacute mountain sickness, sometimes called high altitude pulmonary hypertension, is a subacute or chronic condition. It yields persistent pulmonary

hypertension, leading to right heart failure, dyspnoea, oedema/anasarca, ascites, and hepatomegaly. There are adult and infantile subtypes that are often associated with chronic mountain sickness (León-Velarde et al. 2005).

In chronic mountain sickness (Monge´s disease, chronic soroche), patients typically have polycythaemia and pulmonary hypertension leading to right heart failure. Symptoms include headaches, insomnia, lethargy, dizziness, tinnitus, plethora, polycythaemia, and bone and muscle pain (Hackett and Roach 2004, Reeves and León-Velarde 2004). It affects native (including indigenous) populations and long-term residents living at altitudes exceeding 2500 m.

2.3.1. Prevalence and individual susceptibility

AMS is a common problem at altitude. It affects 25% of those ascending to altitudes of 1850 to 2750 m (Honigman et al. 1993), 42% at altitudes of 3000 m (Hackett and Roach 2001), and even 84% of tourists flying direct to Lhasa (3860 m) without preacclimatization (Barry and Pollard 2003). In a prospective observational study, 84% of people who flew to 3740 m developed acute mountain sickness (Murdoch 1995), while about 50% of trekkers who walk to altitudes higher than 4000 m in the same region over five or more days got AMS. In the Himalayas in Nepal, the incidence of AMS has been reported to be 0% at 2500 to 3000 m, 10% at 3000 to 4000 m, 15% at 4000 to 4500 m, 51% at 4500 to 5000 m, and 34% over 5000 m (Vardy et al. 2006). The prevalence of AMS depends on an individual's susceptibility, the rate of ascent, and the absolute altitude achieved (especially the sleeping altitude) (Basnyat and Murdoch 2003). Speed of ascent, exercise during or immediately after ascent, male sex, and youth are all risk factors also (Barry and Pollard 2003).

HACE is said to be rare and usually occurs only at altitudes over 4000 m (Imray et al. 2011). The incidence of HACE is much lower than for AMS, with estimates in the range 0.1-4.0% (Basnyat and Murdoch 2003). In two observational field studies at altitudes from 3350 to 5000 m, 1.2-1.8% developed HACE (Singh et al. 1969, Hackett et al.1976). Among the Gosainkund pilgrims in the Nepalese Himalayas at 4300 m, the incidence of HACE has been reported to be 31% (Basnyat et al. 2000b). Ataxia has been mentioned as an early sign of impending HACE, and its incidence at 4505 to 4779 m is 0.26% (Wu et al. 2006). HAPE usually occurs above 2500 m, but it has also been recognised at altitudes between 1500 m and 2500 m (Gabry et al. 2003). The prevalence of HAPE depends on the degree of susceptibility, the rate of ascent, and the final altitude. Its incidence is 0.0001% at 2700 m, increasing to 2% at 4000 m (Barry and Pollard 2003). At an altitude of 4500 m, the prevalence may vary depending on the rate of ascent between 0.2 and 6% in an unselected population (Bärtsch et al. 2002) and at 5500 m between 2 and 15% (Bärtsch et al. 2005).

An individual's past performance at altitude is the main predictor of their future performance (Imray et al. 2011). Some people are more susceptible to AMS than others and variants of at least eight genetic polymorphisms show positive associations suggesting that acute mountain sickness is an environmentally mediated polygenic disorder. (Imray et al. 2011, MacInnis et al. 2011). Because of the polygenic nature of the human response to hypobaric hypoxia, several genetic loci, each with a small contribution, probably define the phenotype. These genes include the erythropoietin response gene, those that encode for nitric oxide synthase, and those that encode aldosterone synthase and angiotensin converting enzyme polymorphism (MacInnis et al. 2011).

The risk of developing acute mountain sickness was associated with better aerobic capacity, younger age, and higher body mass index (Gallagher and Hackett 2004). Obesity has been shown to be associated with the development of AMS, which may be partly related to greater nocturnal desaturation with altitude exposure (Ri-Li et al. 2003). Higher risk is also associated with living below 900 m altitude (Honigman et al.1993), ascent rate higher than recommendations, acquired altitude, sleeping altitude (Barry and Pollard 2003), and physical stress (Roach et al. 2000). Good aerobic capacity may increase risk if the person does not understand to proceed slowly and peacefully enough at the beginning of the ascent. In some studies, age has a slight protective effect (Silber et al. 2003, Moraga et al. 2008). Over 50-year-olds have a smaller risk for AMS (Honigman et al.1993, Roach et al. 1995). The usual illnesses, such as asthma, diabetes, anemia, and arterial hypertension do not increase the risk (Peacock 1998). The more significant illnesses (for example coronary disease, all the premises that will elevate pulmonary hypertension at sea level, and chronic obstructive pulmonary disease, which weakens hemodynamic and respiration function, can increase the risk for AMS (Barry and Pollard 2003). No clinical feature or test has been shown to predict an individual's susceptibility with any reliability (Imray et al. 2011). Arterial oxygen saturation determined 20-30 minutes after exposure to simulated hypoxia, equivalent to that at 2300-4200 m altitude, seems to be the best predictor of susceptibility (Burtscher et al. 2008). Individuals who develop HAPE at altitudes of 4000 m show an abnormal increase in pulmonary artery pressure during brief or prolonged hypoxic exposure. Interestingly, they also have a greater pulmonary artery pressure rise during exercise in normoxia, pointing to a constitutionally generalized hyper reactivity of the pulmonary circulation. Furthermore, most HAPE-susceptible individuals have a low hypoxic ventilatory response, which leads to a low alveolar PO_2 and thus a greater stimulus to hypoxic pulmonary vasoconstriction at any given altitude (Bärtsch et al. 2005).

The individual risk for AMS among healthy subjects can be estimates to be low in individuals with no prior history of altitude illness and when they are ascending no higher than 2800 m or individuals who are spending more than two days to arrive

at 2500-3000 m altitude with subsequent increases in sleeping altitude below 500 m per day. The risk is moderate among: individuals with prior history of AMS and they are ascending to 2500-2800 m in one day; individuals that have no history of AMS and they are ascending to over 2800 m in one day; or individuals that are ascending more than 500 m per day (increase in sleeping elevation) at altitudes above 3000 m. The risk for AMS is high if: the subjects have a history of AMS and they are ascending to 2800 m or higher in one day; they have a prior history of HAPE or HACE; they are ascending to above 3500 m in one day or ascending more than 500 meter per day above 3500 m. The risk is very high at some mountains or routes where very rapid ascent profiles are common (e.g. Mt. Kilimanjaro) (Luks et al. 2010).

2.3.2. High altitude headache

High altitude headache is defined by the International Headache Society as a headache that develops within 24 hours of ascent above 2500 m and resolves within 8 hours of descent (Imray et al. 2011).

Headache is the most common and most prominent of the altitude related symptoms. A prospective observational study estimated that 80% of people who ascend to high altitudes are affected by high altitude headache (Wilson et al. 2009). Although high altitude headache, and AMS in general, share many characteristics with migraine, the responses of high altitude headache to the 5-hydroxytryptamine agonist sumatriptan have been inconsistent (Burtscher et al. 1995). Unlike a common migraine, high altitude headache resolves after 10-15 minutes of supplementary oxygen therapy (2 L per minute) (Imray et al. 2011).

High altitude headache is so common that it is quite often considered as a part of normal acclimatization. The headache often worsens during the night and with exertion. Most high altitude headaches resolve with mild analgesic treatment (paracetamol or ibuprofen). The person may need to stop the ascent or descend to lower altitude if the headache does not improve with simple analgesia (Imray et al. 2011).

2.3.3. Acute mountain sickness (AMS)

AMS is a non-specific syndrome characterized by the presence of headache and at least one of the following: gastrointestinal symptoms (like loss of appetite, nausea and vomiting), insomnia or difficulty sleeping, dizziness, and weakness or fatigue. It is a self-limiting syndrome, appearing 6-12 hours after arrival at high altitude and usually resolving in 1-3 days if properly treated (rest, descent to lower altitude,

medication etc.), but may sometimes progress to more serious, even life threating mountain sickness, such as HAPE and HACE (Imray et al. 2011). Headache is deemed the cardinal symptom, but the characteristics are not sufficiently distinctive to differentiate it from other causes of headache (Silber et al. 2003). The non-specific symptoms and signs of AMS can result in diagnostic confusion with other disorders, such as exhaustion, dehydration, hypothermia, alcohol hangover, and migraine. (Basnyat et al. 2000a). Many people who usually live at sea level are surprised on their first encounter with acute mountain sickness by debilitating tiredness, which may be compounded by sleeping difficulties. Individuals may note decreased urine output independent of fluid intake (Hackett and Rennie 1979). If the symptoms are ignored or diagnostic signs are absent, and the presence of abnormal neurological or respiratory signs can show progression to or development of HACE or HAPE (Basnyat and Murdoch 2003).

AMS and HACE have similarities in their pathophysiology (Hackett 1999, Roach and Hackett 2001, Bärtsch and Roach 2001). The exact mechanism causing these syndromes is unknown, although evidence points to a process in the central nervous system. The classic theory of the pathogenesis of high altitude headache has been that it results from increased intracranial pressure secondary to hypoxemia in people who have less compliant intracranial volumes (Roach and Hackett 2001). This theory is that AMS and the headache are a consequence of the circulation of the brain which has increased and as a consequence of which the capillary pressure increases, fluid trickles from the capillaries to the tissue, and the brain swells (Roach and Hackett 2001, Basnyat and Murdoch 2003). Hypoxia causes both in the brain and the lungs hemodynamical and nervous reactions, which lead to the excessive perfusion of the capillary blood vessels, rise of capillary pressure, capillary leak, and finally oedema (Hackett and Roach 2001). Relative hypoventilation and impaired gas exchange (Moore et al.1986, Ge et al. 1997), increasing of the sympathetic activity (Bärtsch et al. 1991), and fluid retention and redistribution are typical (Swenson 1997) to the AMS cases. In moderate to severe AMS, raised intracranial pressure is typical (Basnyat and Murdoch 2003).

Several models have been created to explain the pathophysiology of AMS and HACE (Hackett and Roach 2001, Basnyat and Murdoch 2003, Wilson et al. 2011). In Hackett and Roach's model, hypoxemia elicits various neurohumoral and haemodynamic responses that ultimately lead to increased cerebral blood flow, altered permeability of the blood-brain barrier, and cerebral oedema. These changes result in brain swelling and raised intracranial pressure. According to the model, AMS occurs in people who have inadequate cerebrospinal capacity to buffer the brain swelling; those with a greater ratio of cranial cerebrospinal fluid to brain volume are better able to compensate for swelling through displacement of cerebrospinal fluid, and are less likely to develop AMS than people with a lower ratio.

Basnyat and Murdoch presented (2003) that fluid accumulation in the brain may be caused by cytotoxic oedema (cell swelling due to increased intracellular osmolality), vasogenic oedema (leak of the blood-brain barrier with extravasation of proteins and fluid into the interstitial space), or both. In their model, the cytotoxic oedema with increased cerebrospinal-fluid pressure, decreased perfusion, and focal ischemia may occur in the later stages of HACE but it does not explain AMS or early HACE.

The most accepted theory nowadays is that the oedema is vasogenic. The tissue will swell because of the capillary leak when extracellular fluid increases, which then will be followed by the cytotoxic oedema: in other words, the cells will swell from the growth of the intracellular pressure when the oxidation weakens. Changes consistent with vasogenic oedema are evident from HACE-patient MRI findings (Hackett et al. 1998). A vasogenic origin of oedema is alos supported by some animal tests (Krasney 1997) and the response to corticosteroids (Fishman 1975). Several factors, which cannot individually explain the process that triggers vasogenic oedema at high altitude include: raised cerebral capillary pressure resulting in a mechanical vascular leak; impaired cerebral autoregulation in the presence of hypoxic cerebral vasodilatation; and alteration in permeability of the blood-brain barrier because of hypoxia-induced chemical mediators such as bradykinin, histamine, nitric oxide, arachidonic acid, and vascular endothelial growth factor (Basnyat and Murdoch 2003).

This classic theory of the pathogenesis of high altitude headache (that it results from increased intracranial pressure secondary to hypoxemia in people who have less compliant intracranial volumes (Roach and Hackett 2001)) has some problems. There does not appear to be a correlation between the headache of AMS and the presence of cerebral oedema (Bailey et al. 2006, Wilson et al. 2009) and retinal venous distension and the increased venous blood demonstrated by near infra-red spectroscopy, and more recently by MRI, imply that a relative venous insufficiency may exist in hypoxia. Slight increases in central venous pressure (e.g., from hypoxia-induced pulmonary vasoconstriction) may further compromise venous outflow at altitude. Thus, the pathogenesis of headaches may currently be considered to be idiopathic (Wilson et al. 2011).

2.3.4. High altitude cerebral oedema (HACE)

Diagnosis of high altitude cerebral oedema (HACE) has been defined by the Lake Louise committee to include the symptoms of AMS plus gait ataxia or mental status changes, or both ataxia and mental status changes together, regardless of AMS symptoms (Roach et al. 1993). HACE is widely viewed as the end stage of AMS, and is normally preceded by symptoms of AMS. HACE is characterised by altered mental

status, including impaired mental capacity, ataxia, and altered consciousness, which may progress to coma and death due to brain herniation as soon as 24 hours after the onset of these symptoms. People with concomitant HAPE may progress very rapidly from AMS to HACE. Clinical examination may reveal papilledema, ataxia, retinal haemorrhages, and, occasionally, focal neurological deficits (Basnyat and Murdoch 2003, Imray et al. 2011). The proposed pathophysiology of AMS and HACE is presented in Figure 2.

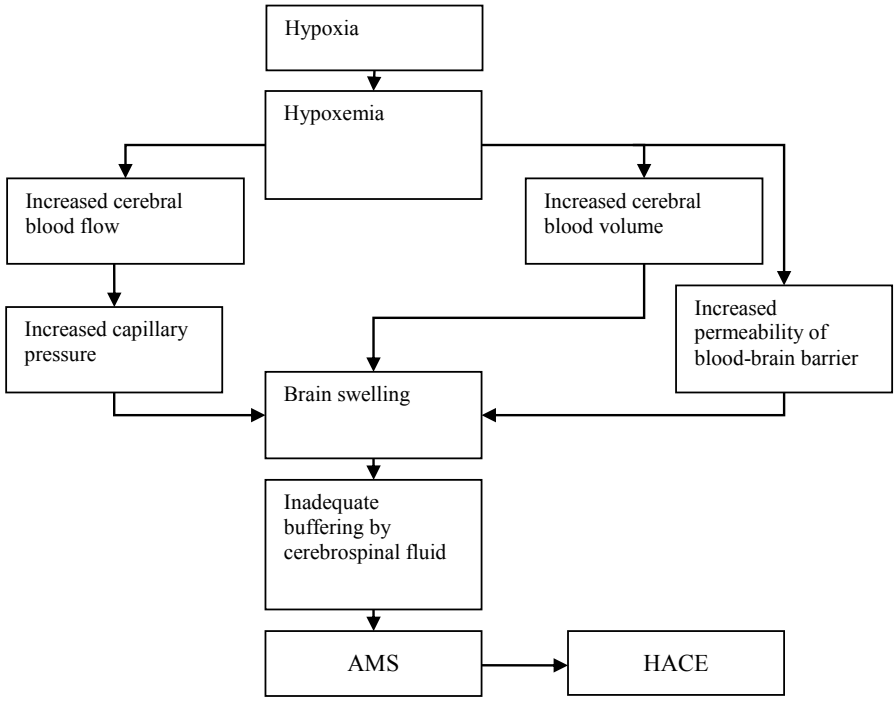


Figure 2. Proposed pathophysiology of AMS and HACE. Adopted from Basnyat and Murdoch 2003, originally in Hackett and Roach 2001.

Portable hyperbaric chambers are effective for treating severe altitude illness (Luks et al. 2010), but they require constant tending by care providers and are difficult to use with claustrophobic or vomiting patients. Symptoms may recur when individuals are removed from the chamber (Luks et al. 2010). Use of a portable hyperbaric chamber should not delay descent in situations where descent is feasible.

2.3.5. High altitude pulmonary oedema (HAPE)

High altitude pulmonary oedema manifests as a non-cardiogenic form of pulmonary oedema and is not necessarily preceded by acute mountain sickness (Imray et al 2011). HAPE occurs most commonly one to five days after arrival at altitudes above 2500 m and consists of dyspnoea with exercise, progressing to dyspnoea at rest, a dry cough, which then becomes productive with blood stained sputum, weakness, and poor exercise tolerance (Maggirorini 2010). As the disease worsens, severe dyspnoea and frank pulmonary oedema are obvious, with coma and death following if the condition is not treated. Physical findings may initially be subtle.

Early clinical signs include tachypnoea and tachycardia at rest as the illness progresses; fever is common, although rarely exceeding 38.3°C. Crackles may be present on auscultation of the chest. HAPE is frequently accompanied by signs of HACE. There is no radiographic feature specific to HAPE and electrocardiography may show evidence of right-ventricular strain (Vock et al.1991, Basnyat and Murdoch 2003).

HAPE may be overrepresented in men compared with women. People with abnormalities of the cardiopulmonary circulation that are associated with increased pulmonary blood-flow pressure, such as unilateral absence of a pulmonary artery or primary pulmonary hypertension, or both, are at increased risk of HAPE, even at moderate altitudes. Exercise and cold lead to increased pulmonary intravascular pressure, and may also be contributing factors to the development of HAPE (Basnyat and Murdoch 2003, Gallagher and Hackett 2004). Other risk factors include: high ascent rate or speed of ascent, exercise during or immediately after ascent, male sex, youth, and individual susceptibility (Barry and Pollard 2003).

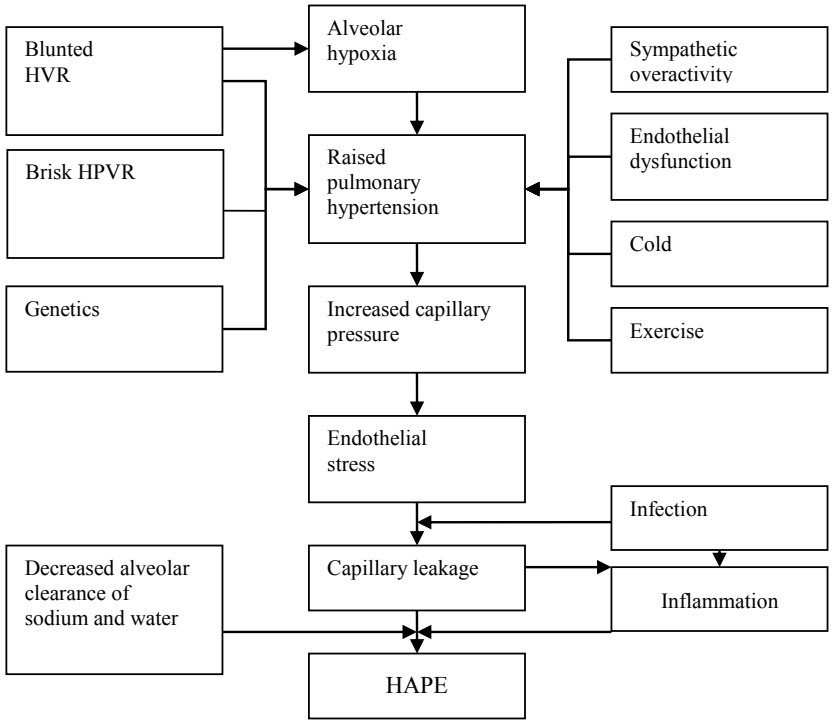
Patients with high altitude pulmonary oedema tend to have lower oxygen saturations than unaffected people at the same altitude, but the degree of desaturation by itself is not a reliable sign of high altitude pulmonary oedema (Sartori et al. 2002). SpO_2 among well acclimatized climbers is normally 80-86% at 4200 m altitude but it can even be 75% for symptomless yet unacclimatized people: at less than 5500 m altitude, values below this are said to be diagnostic of HAPE. At 3500-5500 m, SpO_2 is usually 50-60% for the HAPE patients (Peacock 1998).

The exact mechanism that causes HAPE is still unknown. It is established as the consequence of hypoxic pulmonary vasoconstriction and sufficient transmission of high pulmonary artery pressure and blood flow to portions of the pulmonary capillary bed, most likely due to regional unevenness in hypoxic pulmonary vasoconstriction (Bärtsch et al. 2005). Some characteristics of HAPE include: exaggerated pulmonary hypertension leading to vascular leakage through overperfusion, stress failure, or both (Basnyat and Murdoch 2003). There are several possible causes of the pulmonary hypertension seen in HAPE. The most widely accepted theory is that uneven hypoxic pulmonary vasoconstriction may cause regional overperfusion of capillaries in areas of least arterial vasoconstriction, leading to increased

capillary pressure and leakage (Hultgren 1996, Bärtsch et al. 2005). Endothelial dysfunction may also play a part in causing the excessive pulmonary hypertension of HAPE through impaired release of relaxing factors and augmented release of vasoconstrictors (Basnyat and Murdoch 2003). Exaggerated hypoxic pulmonary vasoconstriction is associated with impaired nitric-oxide synthesis (Busch et al. 2001) and there is a hypothesis that HAPE-susceptible people may have a defect in nitric-oxide synthesis, possibly due to reduced nitric-oxide synthase activity (Droma et al. 2002). A further mechanism that may contribute to the pathophysiology of HAPE is a diminished capacity for alveolar fluid reabsorption and inflammation. It is conceivable that the pressure required for transvascular leakage decreases when the integrity of the alveolar capillary barrier is weakened. Thus any inflammatory process of the respiratory tract that extends to the alveolar space would facilitate oedema formation at lower capillary pressures. Any reduction in the capillary bed should enhance oedema formation because of reduced reserve capacity and thus higher resistance to increased flow (Bärtsch et al. 2005).

Gene polymorphisms that confer differences in the activities of key enzymes may play a part in the pathogenesis of HAPE (Basnyat and Murdoch 2003). HAPE is positively associated with two eNOS gene polymorphisms (G894T-variant and 27-base pair variable numbers of tandem repeats) and HLA-DR6 and HLA-DQ4 alleles, which are associated with vascular diseases such as essential hypertension and coronary heart disease. However, an investigation in Caucasians equivalent to the Japanese study did not find an association between susceptibility to HAPE and a number of eNOS polymorphisms, including the G894T variant or HLA-DR6 and HLA-DQ4 alleles (Bärtsch et al. 2005, Stearn and Grissom 2008).

The proposed pathophysiology of HAPE is presented in Figure 3.



HVR=hypoxic ventilatory response. HPVR=hypoxic pulmonary vascular response.

Figure 3. Proposed pathophysiology of high-altitude pulmonary oedema. Adopted from Basnyat and Murdoch 2003, originally in Schoene et al. 2001.

2.4. SYMPTOMS AND DIAGNOSIS

AMS is diagnosed according to a recent gain in altitude, the presence of headaches, and at least one of the following symptoms: gastrointestinal upset, fatigue, dizziness, or insomnia (Hackett and Oelz 1992). Symptoms of HAPE consist of dyspnoea with exercise, progressing to dyspnoea at rest, and a dry cough which then becomes productive with blood stained sputum. Crackles may be present on auscultation of the chest. Increasing weakness, poor exercise tolerance, profound hypoxemia, and death may occur if the condition is not treated (Barry and Pollard 2003, Imray et al. 2011). Arterial oxygen saturation (SpO_2) has said to be diagnostic for HAPE if it is less than 70% below 5500 m altitude (Peacock 1998) but the degree of desaturation alone is not a reliable sign of high altitude pulmonary oedema (Sartori et al. 2002).

HACE is usually preceded by acute mountain sickness. Headache, nausea and vomiting, hallucination, disorientation, and confusion are often seen; seizures are

less common. Clinical signs include: ataxia, a common early feature that may be disabling and is often the last sign to disappear during recovery; a progressive deterioration in consciousness, proceeding to coma and death; and papilledema and retinal haemorrhages. Focal neurological signs may occur, but in the absence of other signs and symptoms of cerebral oedema these should prompt consideration of other diagnoses (Barry and Pollard 2003). Severe illness due to HACE may develop over a few hours, especially if the prodromal signs are ignored or misinterpreted, and may be accompanied by high altitude pulmonary oedema.

Symptoms of acute mountain sickness are commonly misattributed to viral infection, alcohol hangover, exhaustion, or dehydration. Fever is often absent in acute mountain sickness, however. Use of alcohol or other drugs should be excluded when taking a history. If rest and rehydration do not improve symptoms, fatigue and dehydration are unlikely to be the primary cause. A patient with relevant symptoms who has recently ascended to a new altitude is likely to have altitude sickness, and he should be treated for altitude sickness until another disease process is proven (Imray et al. 2011).

2.4.1. Lake Louise Questionnaire

Symptoms of acute mountain sickness can be quantified by using the Lake Louise Scoring system (LLS) (Table 1), (Roach et al. 1993). It is easy to use and it has been widely adopted for use in the field (Imray et al. 2011). Because LLS was originally designed in 1991 for assessing the severity of symptoms of AMS as an epidemiological research tool, its usefulness to direct the management of an individual case is limited (Imray et al. 2011). The LLS questionnaire was originally made in English; it may not always be understood by those whose first language is not English and may be too complex for use with young children. Fewer symptoms of acute mountain sickness were reported using the standard Lake Louise questionnaire compared with a questionnaire using age appropriate language or visual representations (Southard et al. 2007). Concordantly, a simple visual analogue score has also been reported to be a simple effective measure of the severity of acute mountain sickness (Wagner et al. 2007).

Symptom	Score
1. Headache	
No headache	0
Mild headache	1
Moderate headache	2
Severe, incapacitating	3
2. Gastrointestinal symptoms:	
No gastrointestinal symptoms	0
Poor appetite or nausea	1
Moderate nausea or vomiting	2
Severe nausea and vomiting, incapacitating	3
3. Fatigue/weakness:	
Not tired or weak	0
Mild fatigue/weakness	1
Moderate fatigue/weakness	2
Severe fatigue/weakness, incapacitating	3
4. Dizzy/light-headedness:	
Not dizzy	0
Mild dizziness	1
Moderate dizziness	2
Severe, incapacitating	3
5. Difficulty with sleeping:	
Slept well as usual	0
Did not sleep as well as usual	1
Woke up many times, poor night's sleep	2
Could not sleep at all	3
Clinical assessment:	
6. Change in mental status:	
No change	0
Lethargy/lassitude	1
Disoriented/confused	2
Stupor/semi-consciousness	3
7. Ataxia (heel to toe walking):	
No ataxia	0
Manoeuvres to maintain balance	1
Steps off line	2
Falls down	3
Cannot stand	4
8. Peripheral oedema:	
No oedema	0
One location	1
Two or more locations	2

Table 1. Lake Louise acute mountain sickness questionnaire. An individual has acute mountain sickness as assessed by the Lake Louise self-assessment scoring system (questions 1-5) if they fulfil the following criteria: (1) recent ascent at high altitude, (2) headache present, and (3) the total symptom score above 3 (Hackett and Oelz 1992).

An abbreviated version of the LLS, the Lake Louise AMS Self-Report Score and its application Clinical Assessment Score Questionnaire is easy to use even for non-medical persons (Hackett and Oelz 1992). AMS is diagnosed according to a recent gain in altitude, the presence of headaches, and at least one of the following symptoms: gastrointestinal upset, fatigue, dizziness, or insomnia. Symptoms and clinical findings, such as peripheral oedema, difficulties in walking a line or standing, and changes in mental state, were graded from 0 to 4, with 0 meaning no symptoms and 1 to 4 meaning mild, moderate, severe, and extremely severe symptoms, respectively. A sum for self-reported symptoms of 2-4 points or above, including headache, indicated AMS. The cut of points vary a little bit but usually three points is classified for AMS and four if Clinical Assessment Score is added. The Lake Louise AMS Self-Report Score has become the gold standard of assessing AMS by non-clinicians, including expedition leaders and commercial guides, who often make decisions about a climber's ability to continue trekking (van Roo et al. 2011).

AMS may be classified as either a mild, moderate, or severe form (Luks et al. 2010). AMS may be considered to be mild if there is a headache plus 1 or more other symptom (nausea/vomiting, fatigue, lassitude, dizziness, difficulty sleeping) and all symptoms are of mild intensity. The score for self-reported mild AMS is 2-4, and in moderate to severe forms of AMS it may be 5-15. The clinical diagnosis of HACE is based on worsening AMS symptoms with headache, change in mental status, and ataxia (tested with heel-to-toe walking in a line). High altitude symptoms that fail to meet the criteria of AMS (LLS points 1 or 2) can be defined as high altitude-related symptoms (Rodway et al. 2003).

2.5. PREVENTION AND TREATMENT

2.5.1. Ascent rate

Ascending slowly and allowing time for acclimatisation is the best way of preventing AMS (Basnyat and Murdoch 2003, Stream and Grissom 2008, Imray et al 2011). The gold standard is that above 2500-3000 m ascent should be less than 300-600 m per day, with a rest day for every 1000 m climbed or for every 3-4 days (Hacket and Roach 2001, Basnyat and Murdoch 2003, Luks et al. 2010). In planning the rate of ascent, the altitude at which someone sleeps is considered more important than the altitude reached during waking hours, which means that it is permissible to ascend more than the recommended daily rate, as long as descent is made before sleeping (climb high, sleep low). Determining an ideal ascent rate, however, is difficult, and varies from person to person. Subjects with a prior history of AMS or HAPE should choose a lower ascent rate, and pharmacologic prophylaxis is recommended as adjunctive therapy in some cases.

2.5.2. *Hypoxic preconditioning*

The use of hypoxic pre-conditioning for the prevention of AMS is becoming more common, although currently the supporting evidence base is limited (Imray et al. 2011). A night spent at an intermediate altitude (1500–2500 m) before ascent to high altitude will aid acclimatisation (Basnyat and Murdoch 2003). One to three weeks daily pre-acclimatization in a hypobaric chamber several days before the ascent to altitudes of 4300 m has been shown to reduce incidence and severity of AMS (Imray et al. 2011).

2.5.3. *Pharmacological agents*

Pharmacological prophylaxis may be warranted in some situations. These situations include rapid ascent to altitudes higher than 3000 m (e.g., flying to La Paz, Bolivia, at 3625 m), and for people with increased susceptibility to AMS. In rare circumstances (e.g., military or rescue teams who must ascend rapidly to and perform physical work at altitudes above 3500 m), pharmacological prophylaxis is recommended (Luks et al. 2010). This strategy should be avoided except in these particular or other emergency circumstances that mandate a very rapid ascent.

Acetazolamide is the preferred drug, and in emergency situations consideration can be given to the concurrent use of acetazolamide and dexamethasone (Luks et al. 2010, Imray et al. 2011). The recommended adult dose for prophylaxis is 125 mg twice daily (Table 2). The pediatric dose (< 12 yrs) of acetazolamide is 2.5 mg/kg per dose (maximum 125 mg per dose) every 12 hours (Luks et al. 2010). The recommended adult doses for dexamethasone are 2 mg every 6 hours or 4 mg every 12 hours. Very high doses (4 mg every 6 hours) may be considered in very high risk situations, such as military or search and rescue personnel being airlifted to altitudes greater than 3500 m with immediate performance of physical activity, but should not be used outside these limited circumstances. The duration of use should not exceed 10 days (Luks et al. 2010). For individuals ascending to and staying at the same elevation for more than several days, prophylaxis may be stopped after 2 to 3 days at the target altitude or once descent is initiated (Luks et al. 2010).

Nifedipine (30 mg extended release form orally once or twice daily) (Bärtsch et al 1991), phosphodiesterase-5 inhibitors sildenafil (40 mg 3 times daily) and tadalafil (10 mg twice daily), and inhalation of the beta-adrenergic agonist salmeterol (125 μg twice daily) reduce the risk of developing HAPE in HAPE-prone individuals (Stream and Grissom 2008). Because phosphodiesterase-5 inhibitors may worsen AMS symptoms, including headache, and this has not been verified in large studies, cautious use may be an acceptable alternative for selected individuals who have already been observed to tolerate these drugs without ill effects. (Stream and Grissom 2008, Luks et al. 2010).

The usefulness of Ginko biloba products is unclear. While some studies have described its benefits, others found it to be ineffective compared with acetazolamide and placebo (Imray et al. 2011). Other options like chewed coca leaves, coca tea, and other coca-derived products have never been systematically studied (Luks et al 2010).

In low-risk situations, prophylactic medications are not necessary and individuals should rely on a gradual ascent profile. Prophylactic medications should be considered in addition to gradual ascent for use in moderate- to high-risk situations (Luks et al 2010).

Medication	Indication	preventive dosage	treatment dosage
Acetazolamide	AMS, HACE	Oral 125 mg twice per day	Oral 250 mg twice per day*
Dexamethasone	AMS, HACE	Oral 2 mg every 6 h or 4 mg every 12 h	Oral IV, IM AMS: 4 mg every 6 h HACE: 8 mg once then 4 mg every 6 h
Nifedipine	HAPE	Oral 30 mg SR version, every 12 hours or 20 mg of SR version every 8 h	Oral 30 mg SR version, every 12 hours or 20 mg of SR version every 8 h
Sildenafil	HAPE	Oral 50 mg every 8 h	No recommendations, preventive dosage have used
Tadalafil	HAPE	Oral 10 mg twice per day	No recommendations, preventive dosage have used
Salmeterol	HAPE	Inhaled 125 µg twice per day	
Oxygen		Usually only at > 8000 m expeditions, 2-4 litres/min by mask or nasal cannulas	2-4 litres/min by mask initially, then 1-2 litres/min or titrate dose until SaO_2 > 90 %
Portable hyperbaric chamber, Gammow bag®			Depends on model; 13-26 kPa for a minimum of 2 hrs.; continued as long as necessary
Descent	AMS, HACE, HAPE	ascend only 300-600 m per day and to have an acclimatization day for every 1000 m of altitude gained	500 m at least, in mild cases stop, rest and acclimatize 1-2 days

AMS = acute mountain sickness; HACE = high altitude cerebral oedema; HAPE = high altitude pulmonary oedema; SR = sustained release; IV = intravenous; IM = intramuscular.
* Acetazolamide can also be used at this dose as an adjunct to dexamethasone in HACE treatment, but dexamethasone remains the primary treatment for that disorder.

Table 2. Recommended dosages for medications used in the prevention and treatment of altitude illness (Imray 2011, Barry and Pollard 2003, Luks et al. 2010).

2.5.4. Treatment

The principles of treatment for AMS are to avoid further ascent until symptoms have resolved, to descend if there is no improvement or if symptoms worsen, and to descend immediately at the first signs of cerebral or pulmonary oedema.

When practical, an accompanied descent of 300-1000 m remains the most effective treatment for all high altitude illnesses. Other treatments for acute mountain sickness reflect the varying severity of the clinical symptoms. Rest alone is frequently sufficient for mild AMS (LLS 2-4) with maintenance of hydration and combined with symptomatic relief of headache with paracetamol or ibuprofen (Imray et al. 2011). Additional pharmacotherapy may be used in conjunction with the treatments above, especially if descent is impossible and oxygen is unavailable. The useful medications and dosages are presented in Table 2.

For moderate to severe acute mountain sickness (LLS 5 or more) acetazolamide, dexamethasone, or both are the best acute therapy, provided that the patient has not taken these drugs prophylactically (Luks et al. 2010). Analgesics and antiemetics may afford symptomatic relief. Descent and oxygen are the treatments of choice for moderate to severe AMS. Even a small descent of 400–500 m may be sufficient to relieve symptoms (Stream and Grissom 2008). Individuals should descend until symptoms resolve, unless impossible due to terrain. Symptoms typically resolve following a descent of 300 to 1000 m, but the required descent will vary between persons. Individuals should not descend alone, particularly in cases of HACE (Luks et al. 2010). Oxygen delivered by nasal cannula at flow rates sufficient to raise arterial oxygen saturation (SpO_2) to greater than 90% provides a suitable alternative to descent (Stream and Grissom 2008, Luks et al. 2010). Use is not required in all circumstances and is generally reserved for severe cases when descent is not feasible. The supply of oxygen may be limited at remote high altitude clinics or on expeditions, necessitating careful use of this therapy.

The most reliable treatment for HAPE is immediate descent (at least 500 to 1000 m), supplemental oxygen, or both (Stream and Grissom 2008). Oxygen should be provided at a high enough fraction of inspired oxygen to achieve an arterial oxygen saturation of greater than 90% (Stream and Grissom 2008, Luks et al. 2010). If oxygen is not available and descent is unsafe or impossible, a portable hyperbaric chamber can simulate a descent of 1500-2000 m and is a good temporizing measure before definitive therapy is possible with descent to a lower altitude (Luks et al. 2010). Optimal therapy includes ensuring passive descent and keeping the patient warm, which will minimize any additional exercise- or cold-induced sympathetic contribution to the condition (Stream and Grissom 2008). Continuous positive airway pressure may also be useful for the treatment of HAPE; a portable device has been developed that can be used in the mountains. Slow release nifedipine may be useful as an adjunct to descent and oxygen (Stream and Grissom 2008, Luks et al. 2010) (Table 2).

3. PREDICTION OF AMS

Many researchers have looked for ways to predict AMS. Low hypoxic ventilatory response (HVR) has been proposed as a marker of susceptibility to AMS (King and Robinson 1972, Moore et al. 1986), but some field studies have found no connection between HVR and AMS (Sutton et al. 1976, Hohenhaus et al. 1995, Bärtsch et al. 2002). Very high HVR has been reported in successful climbers at extreme altitudes (West 2000), but the high HVR is not necessary for successful climbing after acclimatization to extreme altitudes (Bernardi et al. 2006). In addition, low end-expiratory PO_2 in normoxia (Savourey et al. 1995), a short breath-holding time and increased gag reflex (Austin and Sleigh 1995), ventilation changes during brief normobaric hypoxia (Schirlo et al. 2002), or changes in SpO_2 during short term exposure for normobaric or hypobaric hypoxia (Burtscher et al. 2008) would enable the detection of those climbers who are susceptible to AMS.

Monitoring heart rate (HR) and arterial oxygen saturation at rest (R-SpO_2) have been proposed as simple indicators of inadequate acclimatisation to high altitudes and impending AMS (Roach et al. 1998, Burtscher et al. 2008). SpO_2 value after light exercise has been shown to be a convenient means of estimating the level of high-altitude acclimatization among healthy subjects (Saito et al. 1995). Previously, normo- and hypobaric exercise tests have been shown to indicate susceptibility to AMS. Savourey et al. proposed arterial oxygen content (CaO_2), based on haemoglobin concentration and SaO_2 by pulse oximetry during submaximal exercise after 30 min in hypoxia as a good predictor of impending AMS (Savourey et al. 2007). Similarly, oxygen saturation during exercise in the early hours of exposure at 4300 m has been found to correlate with the subsequent development of impending AMS (Staab et al. 2006). Arterial oxygen saturation measurement during, or immediately after, exercise has been shown to be useful in anticipating AMS (Roach et al. 1998), but it is susceptible to many disruptive factors (for example temperature) (Luks and Swenson 2011). Changes in heart rate variation (HRV) parameters during acclimatization and AMS at 3180-4559 m altitudes have been shown in several studies (Loeppky et al. 2003, Lanfranchi et al. 2005, Chen et al. 2008, Huang et al. 2010). Modesti et al. generated a predictive index combining clinical and haematological parameters (oxygen saturation, haematocrit, day of expedition, and maximum velocity of clot formation) measured at an intermediate step on the way to the top to predict AMS within 48 h of reaching high altitude (Modesti et al. 2011). In the work described here, however, SpO_2 and HRV measurements are utilized as a predictor of AMS, given their practical usefulness in the field (*vide infra*).

3.1. OXYGEN SATURATION (SPO_2)

The O_2 delivery system in the body consists of the lungs and the cardiovascular system. O_2 delivery to a particular tissue depends on the amount of O_2 entering the lungs, the adequacy of pulmonary gas exchange, correct ratio of ventilation/perfusion, the blood flow to the tissue, and the capacity of the blood to carry O_2. The amount of O_2 in the blood is determined by the amount of dissolved O_2, the amount of haemoglobin in the blood, and the affinity of the haemoglobin for O_2 (Ganong 1983). Oxygen saturation (SpO_2) is a relative measure of the amount of oxygen that is dissolved or carried in a blood. Oxygen saturation can be measured regionally and non-invasively. Arterial oxygenation is commonly measured using pulse oximetry. A pulse oximetry monitor displays the percentage of arterial haemoglobin in the oxyhemoglobin configuration. Acceptable normal ranges for healthy subjects are from 95 to 99%. A pulse oximetry sensor is placed on a thin part of the patient's body, usually a fingertip. Light of two different wavelengths is passed through the tissue to a photo detector. The changing absorbance at each of the wavelengths is measured, allowing determination of the absorbances due to the pulsing arterial blood alone, excluding venous blood, skin, bone, muscle and fat (Severinghaus et al. 1987). In addition, peripheral tissue saturation can be measured using near-infrared spectroscopy, which makes it possible to measure both oxygenated and deoxygenated haemoglobin in both brain and muscle in various environmental conditions (Peltonen et al. 2007, Peltonen et al. 2009).

3.1.1. SpO_2 normally at rest and exercise

When blood is equilibrated with 100% O_2 (PO_2 = 760 mm Hg), the haemoglobin becomes 100% saturated. *In vivo* at sea level, the haemoglobin in systemic arterial blood is only 97% saturated due to a slight admixture with venous blood that bypasses the lungs ("physiologic shunt") (Ganong 1983).

At sea level, both an excessive alveolar-to-arterial PO_2 difference (A-a DO_2) (> 25-30 Torr) and inadequate compensatory hyperventilation (arterial PCO_2 > 35 Torr) commonly contribute to exercise-induced arterial hypoxemia, as do acid- and temperature-induced shifts in O_2 dissociation at any given arterial PO_2. In turn, expiratory flow limitation may present a significant mechanical constraint to exercise hyperpnoea, whereas ventilation-perfusion ratio maldistribution and diffusion limitation contribute about equally to the excessive A-a DO_2 (Dempsey and Wagner 1999).

3.1.2. SpO_2 at altitude

The human body performs best at sea level, where the atmospheric pressure is 101,325 Pa or 1013.25 millibars (or 1 atm, by definition). The concentration of O_2 in sea-level air is 20.9%, so the partial pressure of O_2 (PO_2) is 21.136 kPa. Atmospheric pressure decreases exponentially with altitude while the O_2 fraction remains constant to about 100 km, so PO_2 decreases exponentially with altitude as well. It is about half of its sea-level value at 5000 m, the altitude of the Everest Base Camp, and only a third at 8848 m, the summit of Mount Everest (Barry and Pollard 2003). At high altitude, the air is very dry but the alveolar pressure of H_2O (PH_2O) remains 47 mmHg in every altitude because the respiratory system depends only on the temperature to maintain alveolar air humidity at 100%. The PH_2O takes a relatively bigger part from total alveolar air pressure at high altitude than at sea level. This leads to the relatively more significant decrease to an intra-alveolar PO2 than what would be caused by the relative decrease of the air pressure.

The most important contributor to the maintenance of arterial oxygen content (CaO_2) during acclimatization is involuntary increase in ventilation. A drop in the PO_2 of the arterial blood leads to hypoxic stimulation of peripheral chemoreceptors, located primarily in the carotid and aortic bodies, causing an increase in the depth and rate of breathing. This phenomenon is known as the hypoxic ventilator response. Increased ventilation lowers the alveolar PCO_2 and increases the alveolar PO_2 (Palmer 2010). At extreme altitudes, like at the summit of Mount Everest, alveolar ventilation is increased approximately 5-fold, such that the PCO_2 is reduced to 7 to 8 mm Hg (West 2000). This extreme degree of ventilation limits the fall in PO_2 to around 35 mm Hg, even though the inspired PO_2 is only 29% that of sea level (Palmer 2010). SpO_2 decreases when altitude increases and marked hypoxemia occurs, maximum aerobic power is depressed and this impairs the ability to work maximally. SpO_2 varies over a range in normal individuals at a given altitude. It is usually lower on first arrival at a given altitude and rises somewhat with acclimatization (Mason et al. 2000; Botella de Maglia and Compte Torrero 2005; Compte-Torrero et al. 2005).

3.1.3. SpO_2 as a predictor of AMS

R-SpO_2 varies in normal individuals at a given altitude (Mason et al. 2000, Compte-Torrero et al. 2005, Botella de Maglia and Compte Torrero 2005). It has been shown that resting arterial hypoxemia is related to later development of clinical AMS (Hackett et al. 1982) and oxygen saturation at rest correlates inversely with the Lake Louise AMS score at 4200 m and 2659 m (Roach et al. 1998, Kao et al. 2002). Rathat and colleagues (1992) suggested that measuring changes in SpO_2 at rest and after 5-min exercise (50 % of normoxic $\dot{V}O_2max$) in normoxia and hypoxia (0.115 FiO_2) could distinguish individuals who are susceptible to AMS. The predictive value

of SpO_2 measurements and an association between decreased oxygen saturation and AMS have been shown at an altitude of 4200m (Roach et al. 1998) and 2659 m (Kao et al. 2002). However, some other studies did not demonstrate such an association (O'Connor et al. 2004, Wagner et al. 2012, Chen et al. 2012). SpO_2 value after light exercise (Ex-SpO_2) has been shown to be a convenient means of estimating the level of high-altitude acclimatization among healthy subjects (Saito et al. 1995). Savourey et al. (2007) proposed arterial oxygen content (CaO_2), based on haemoglobin concentration and SpO_2 by pulse oximetry during submaximal exercise after 30 min in hypoxia as a good predictor of impending AMS. Similarly, oxygen saturation during exercise in the early hours of exposure at 4300 m has been found to correlate with the subsequent development of impending AMS (Staab et al. 2006). Peripheral arterial desaturation is further exacerbated by exercise in adolescents with AMS (Major et al. 2012). Ex-SpO_2 measurements after the 6-minute walk test have been shown to predict a successfull climb to reach the summit of Aconcagua (Lazio et al. 2010).

3.2. HEART RATE VARIABILITY (HRV)

The autonomic nervous system (ANS) is the part of the nervous system that controls the body's visceral functions, including action of the heart and vascular tone. Part of the function of the ANS emphasises autonomic reflexes, whilst part of it is under central regulation. It is in close connection with the humoral system modulating hormonal responses and it is an essential part of the generalised stress reaction, inducing and modifying it. The ANS can be divided in sympathetic and parasympathetic branches.

Sympathetic stimulation activates the "fight or flight" reaction by increasing heart rate, blood pressure, and blood flow to brain, heart, lungs, and skeletal muscle. It also dilates pupils and the bronchial tree, and increases renin secretion in the kidneys (Ruffolo 1991). The parasympathetic nervous system acts in the opposite way to the sympathetic system. Activation of the parasympathetic nervous system results in decreased heart rate and inotropy, increased salivation, increased motility of the gastrointestinal tract, constriction of the bronchial tree, contraction of the pupils, and relaxation of the bladder (Ruffolo 1991). Hypoxia elicits neurohumoral and hemodynamic responses in the brain and lungs, resulting in overperfusion of microvascular beds, elevated hydrostatic capillary pressure, capillary leakage, and consequent edema (Hackett and Roach 2001). On the other hand, hypoxia, exercise, and cold environment have been shown to increase the vasoconstriction in pulmonary circulation (Gallagher and Hackett 2004). Individuals with acute altitude sickness hypoventilate (Moore et al. 1986), their sympathetic activation

is elevated (Mazzeo et al. 1995), and ventilatory drive in response to hypoxia is reduced (Barry and Pollard 2003).

3.2.1. Physiological background of HRV

Heart rate is a product of balance between intrinsic cardiac pacemaker activity and external control mechanisms (Singer et al. 1988). These control mechanisms include the ANS with predominant vagal activity during normal conditions (Kleiger et al. 1991), humoral (renin-angiotensin -system, catecholamines) and thermoregulatory factors (Van Raveswaaij-Arts et al. 1993). In normal conditions, the influence of the control mechanisms increases fluctuation around the intrinsic regular heart rate (Kleiger et al. 1991, Van Raveswaaij-Arts et al. 1993).

Normal variability in heart rate, therefore, is due to the synergistic action of the two branches of the ANS, which act in balance through neural, mechanical, humoral, and other physiological mechanisms to maintain cardiovascular parameters in their optimal ranges and to permit appropriate reactions to changing external or internal conditions. The estimated heart rate of a healthy person at any point in time represents the net effect of the parasympathetic nerves, which slow heart rate, and the sympathetic nerves, which accelerate it. Emotions, thoughts and physical activity have an influence on these changes. Changing heart rhythms also affect the brain's ability to process information, including decision-making, problem-solving, and creativity. The changes also affect the way a person feels (Van Raveswaaij-Arts et al. 1993).

3.2.2. Analysis of HRV

Heart rate variation has been analysed in clinical medicine and in research since the beginning of the 1970s (Antila 1979). The earliest methods were time domain analyses (Van Raveswaaij-Arts et al. 1993, Task Force 1996), followed by power spectral analysis, and non-linear dynamic methods that have been widely used in clinical medicine.

Time domain analysis

Time domain measures are perhaps the simplest way to analyse variations in heart rate. The measured variables are the mean interval between normal QRS-complexes (mean RR (NN)-interval), mean HR, the difference between longest and shortest NN-interval, and the difference between day and night heart rate. More complex

measures can be calculated using statistical time domain methods and geometrical methods. The recommended recording period is 24 h but should be for at least 5 min. (Van Raveswaaij-Arts et al. 1993, Task Force 1996).

Statistical methods can be divided into two classes; those derived from direct measurements of the NN-intervals or instantaneous HR, and those derived from the differences between NN-intervals. The standard deviation of the NN intervals (SDNN) is used in 24-hour recordings (Van Raveswaaij-Arts et al. 1993, Task Force 1996). SDNN reflects all the cyclic components that are responsible for variability during the recording period or the smaller segment used for calculation. The shorter the recording period, the shorter is also the cycle length that SDNN estimates. The variance of HRV also increases with the length of the recording period. SDNN is not a good statistical quantity due to its dependence on the length of the recording period. The standard deviation of the mean NN-interval is used for successive 5-minute recordings. It estimates the changes in heart rate due to cycles longer than 5 min. SDNN index is the mean of the 5-min SDNN and measures the changes due to cycles shorter than 5 min (Van Raveswaaij-Arts et al. 1993, Task Force 1996). The square root of the mean squared differences of successive NN-intervals (RMSSD) correlates well with the HF power of power spectral analysis. The most important limit of the statistical methods used is that they detect only high-frequency variations originating from changes in ANS activity (Van Raveswaaij-Arts et al. 1993, Task Force 1996).

Series of NN intervals can be converted into a geometric pattern and a simple formula is used to estimate the variability based on the properties of the resulting pattern. Generally, there are three possibilities that can be used in geometrical methods. First, a basic measurement of the geometric pattern is converted into the measure of HRV. Second, the geometric pattern is interpolated by a mathematically defined shape and the parameters of this shape are used as measures of HRV. Third, the geometric shape is classified into several pattern-based categories which represent different classes of HRV (Van Raveswaaij-Arts et al. 1993, Task Force 1996).

HRVtriind is the HRV triangular index and it is the integral of the density distribution (the number of all NN intervals) divided by the maximum of the density distribution (number of NN intervals in the modal bin). The numbers explained in the brackets can be used as an approximation when the measurement of NN intervals is on a discrete scale. The number of NN intervals is dependent on the length of the bin, that is, the precision of the discrete scale of measurement. The triangular interpolation of NN interval histogram is the baseline width of the distribution measured as a base of a triangle, which is fitted to the histogram and approximates the NN interval density distribution. The triangle is found based on the minimum square difference to the original NN interval density distribution. (Van Raveswaaij-Arts et al. 1993, Task Force 1996). Geometrical methods are quite insensitive to

the analytical quality of the series of NN intervals, but there must be rather many NN intervals to construct a geometric pattern, thus a recording should be at least 20 min. (Van Raveswaaij-Arts et al. 1993, Task Force 1996).

Frequency domain analysis

In power spectral analysis, the lengths of successive normal RR intervals (RRI, in milliseconds) are plotted against time as a tachogram. Variation of respiratory frequency and arrhythmias change the stationary of RR intervals and influence the analysis. Thus, standardisation of respiratory frequency is obligatory to receive stationary conditions (Task Force 1996).

The mathematical transformation (Fast Fourier Transform) of HRV data into power spectral density is used to discriminate and quantify sympathetic and parasympathetic activity and total autonomic nervous system activity (Van Raveswaaij-Arts et al. 1993, Task Force 1996). Power spectral analysis provides the basic information of power distribution as a function of frequency. The methods to calculate power spectral density can be divided into non-parametric and parametric. The non-parametric methods use quite an easy algorithm and the processing is fast. The parametric methods, like methods based on autoregressive models, provide smoother spectral components which can be distinguished independently of pre-selected frequency bands, easy post-processing of the spectrum with an automatic calculation of high and low frequency power components, and easy identification of the central frequency of each component. Furthermore, the estimation of power spectral density is accurate even on a small number of samples. (Van Raveswaaij-Arts et al. 1993, Task Force 1996).

Three main spectral components are distinguished in a spectrum calculated from short-term recordings of 2 to 5 min: very low frequency (VLF, 0-0.04 Hz), low frequency (LF, 0.04-0.15 Hz), and high frequency (HF, 0.15-0.4 Hz) components. Measurement of VLF, LF, and HF components is usually made in absolute values of power, but LF and HF can also be measured in normalized units (n.u.). Normalized units are calculated by dividing the absolute power of a certain bandwidth with the total spectral power minus VLF component. The LF/HF-ratio is also commonly used to describe the balance of ANS. When analysing long-term recordings, the power spectral density also includes an ultra-low frequency component (ULF, 0-0,003 Hz) (Task Force 1996).

According to the Task Force of the European Society of Cardiology, the preferred duration of ECG recordings for computing short-term HRV components is 5 minutes. The recording should last at least 10 times the wavelength of the lowest frequency bound of the investigated component. Thus a recording of approximately

1 minute is needed to assess the HF and approximately 2 minutes are needed to address the LF component (Task Force 1996).

Poincaré plot analysis

Poincaré plot (or Lorenz plot) analysis is a nonlinear method for HRV analysis and it gives a visual and quantitative analysis of RR-intervals. Quantitative analysis of the Poincaré plot is usually performed by calculating the standard deviation along two diagonal axes, one of them being the line of identity at 45° to the normal axis and it separately measures instantaneous short-term (beat-to-beat) variability (SD1), long-term continuous variability of all RR -intervals (SD2), and the SD1/SD2 ratio (Raetz et al 1991). A strong positive correlation exists between SD1 and the HF power of power spectral analysis at rest, suggesting that SD1 reflects vagal efferent activity. This correlation is weaker during increased sympathetic activity, however. On the other hand, SD2 correlates with LF and LF/HF ratio during exercise (Tulppo et al. 1996). SD1/SD2.ratio reflects sympathovagal balance.

3.2.3. HRV as a predictor of AMS

The exact mechanism causing AMS is unknown, but marked increase in peripheral sympathetic activity is a common feature of AMS and may be involved in the pathogenesis of HAPE (Duplain et al. 1999, West 2004). Heart rate variability reflects sympathetic and parasympathetic, i.e. autonomic nervous system regulation of HR. Several studies have shown a transient reduction in parasympathetic and increased sympathetic activity during acute exposure to hypobaric hypoxia (Sevre et al. 2001, Saito et al. 2005, Hainsworth et al. 2007), which tended to be reversed with acclimatization (Cornolo et al. 2004).

Under hypobaric conditions, a decrease in mean spectral power of R-R intervals was noted within both LF and HF frequency ranges, compared with the study performed in normobaria (Zuzewicz et al. 1999). A reduced R-R variability and relative increase in LF component at high altitude have been noted in several studies (Kanai et al. 2001, Bernardi et al. 1998, Hughson et al. 1994). Deterioration of cardiac autonomic function measured by HRV has been estimated to be more sensitive in the prediction or detection of AMS than clinical symptoms alone at high altitudes (Saito et al. 2005). Loeppky et al. showed in 2003 that AMS is accompanied by increased LF/HF at simulated altitude. In addition, the LF power in normalized units was lower in their study in subjects with AMS at an altitude of 4559 m. Huang et al. estimated in 2010 that low HF power in normalized units or high LF/HF at 1300 m altitude could predict AMS at 3440 m altitude and LF power in normalized

units has been shown to be lower in subjects with AMS (Lanfranchi et al. 2005, Huang et al 2010). Chen et al. demonstrated in 2008 that SDNN, LF, HF, and HF power in normalized units decreased significantly, but LF power in normalized units and LF/HF increased significantly in subjects irrespective of AMS at 3180 m altitude (Chen et al. 2008). In contrast, Koehle et al. and Wille et al. did not find HRV measurements useful for the diagnosis of AMS at 4380 m or 5500 m (Koehle et al. 2010, Wille et al. 2012).

4. CONCLUSION OF THE LITERATURE REVIEW

Acute mountain sickness (AMS) is a common problem while ascending at high altitude. AMS may progress rapidly with fatal results if the acclimatization process fails or symptoms are neglected and the ascent continues. It affects 25% of those ascending to altitudes of 1850 to 2750 m (Honigman et al. 1993), 42% at altitudes of 3000 m (Hackett and Roach 2001), and even 84% of those attempting Lhasa, Tibet (3860 m) by flying (Barry and Pollard 2003). The most common reason for altitude illness is too rapid ascent. There is a need for a non-invasive, specific, and convenient method in field conditions for the detection of inadequate acclimatization and impending AMS. Arterial oxygen saturation (SpO_2) measurement is useful in anticipating AMS (Roach et al. 1998), but it is susceptible to many disruptive factors in the field (for example temperature) (Luks and Swenson 2011). Autonomic cardiac response to increasing altitude could be a low-cost non-invasive test to predict impending AMS, in addition to helping distinguish those who are at risk for AMS and those who are acclimatizing well. Measuring acute hypoxic ventilatory response before altitude exposure helps to estimate the adaptive processes of the climber but does not offer a practical tool for expeditions to predict AMS and control the ascent rate. Even SpO_2 and HRV measurements did not offer an easy solution for predicting AMS (Chen et al. 2012, Wille et al. 2012), but they may offer a practical tool for future expedition medics or leaders. Until such approaches are proven, prevention is the safest and the most efficient method in the care of AMS. Possibilities for medical treatment and oxygen substitution might be limited. Realising the risk of mountain sickness, active inquiry about symptoms and correctly timed reaction to them, in other words interrupting the ascent or descending, helps to reduce and even to prevent the development of serious problems.

AIMS OF THE STUDY

The main aims of this thesis were to evaluate the prevalence of AMS in one of the most popular 6000 m peaks (study I), and evaluate some predicative measurements for AMS like SpO_2 and HRV in hypobaric and hypoxic environments (study II-III). Two AMS cases and their treatment in the field were also presented (study IV).

The specific aims of this work were:

1. To assess the prevalence of the signs and symptoms of acute mountain sickness among Finnish travellers climbing Mount Kilimanjaro, Tanzania (I),

2. To investigate if post-exercise oxygen saturation (Ex-SpO_2) at high altitudes predicts AMS better than R-SpO_2 or resting HR alone (II),

3. To evaluate if HRV level or HRV changes have a relationship to AMS during ascent and provide new information on the deterioration of cardiac autonomic function as measured by HRV not only at altitudes between 2400 and 5000 m, which are most frequent among climbers, but also at extreme altitudes above 5000 m in field conditions (III),

4. To generate tools for AMS for non-medical persons to estimate the risk in field conditions (II-III), and

5. To describe a typical AMS case and the difficulties to treat AMS in the field (IV).

MATERIAL AND METHODS

An observational study to investigate the incidence of AMS experienced by Finnish travellers during their Kilimanjaro treks was carried out at Kilimanjaro, Tanzania (I). The experimental studies in field conditions were carried out during seven expeditions to Denali (Denali 1, Denali 2, Alaska), Shisha Pangma (Tibet), Ulugh Muztagh (Tibet), Island Peak, and Mount Everest (Nepal and Tibet) (II-III). The ascent profiles during measurements for different expeditions are presented in Figure 4. The subjects for case study (IV) were from Shisha Pangma and Ulugh Mustagh expeditions.

1. THE MOUNTAINS

The peak of Kilimanjaro is 5895 m above sea level and 03.04° south in latitude (Coordinates are 3°4′33″S, 37°21′12″E). There are several routes to the summit and the easiest and the most popular is the so-called Marungu Route, where the study was conducted. Most Finnish tour operators represented in the area arrange treks via this route. The distance between the entrance and the summit is 36 km and there are several camps and huts along the route. Most trekkers end their climb at Gillman's Point, which is on the crater rim at 5681m. Some of them continue around the rim to Uhuru Peak (5895 m), the highest point in Africa. These treks normally take six days from the Marungu gate (altitude 1800 m) to the summit and back. Regular camps are Mandara hut (2743 m), Horombo hut (3760 m), and Kibo hut (4730 m). Usually there is a rest and acclimatisation day at Horombo hut.

Denali (Mount McKinley) (Coordinates are 63°04′10″N, 151°00′27″W) is situated in Alaska, United States and it is the highest mountain peak in North America, with a summit elevation of 6194 m above sea level. The mountain is regularly climbed today; in 2003, around 58% of climbers reached the top. But by 2003, the mountain had claimed the lives of nearly 100 mountaineers over time (Coombs and Washburn 1997). The vast majority of climbers use the West Buttress Route and climbers typically take two to four weeks to ascend the mountain. The mountain is characterized by extremely cold weather. According to the National Park Service, the lowest temperature that had been recorded was approximately −73 °C. In June 2002, a weather station was placed at the 5800 m level. The weather station recorded temperatures as low as −59.7 °C on December 1, 2003. On the previous day, November 30, 2003, a temperature of −59.1 °C combined with a wind speed of 8.2 m/s to produce a North American record wind-chill of −83.4 °C. Temperatures as low as −30.5°C and wind-chill as low as −50.7°C have

been recorded by this weather station, even in July (http://en.wikipedia.org/wiki/Mount_McKinley 4.11.2011). The measurements of this study were made at West Buttress Route during two expeditions at May 2001.

Shisha Pangma (Xixabangma) is the fourteenth-highest mountain in the world (8013 m) and is located in south-central Tibet, a few kilometres from the border with Nepal (Coordinates are 28°21′8″N, 85°46′47″E). Shisha Pangma is one of the easier eight-thousanders to climb. The standard route ascends from the north side, and boasts relatively easy access, with vehicle travel possible to base camp at 5000 m (Carter 1985). The measurements of this study were made during a Finnish expedition in May 2002.

Ulugh Muztagh, also known as Ulugh Muztag and Muztag Feng, is an extremely remote mountain group on the Northern Tibet plateau. Located on the border between the Tibetan Autonomous Region and Xinjiang Uyghur Autonomous Region, it is part of the main range of the Kunlun Mountains of Central Asia. (Coordinates are 36°24′45″N, 87°23′06″E).

For a long time its elevation was thought to be as high as 7723 metres, but it was measured by a 1985 Sino-American first ascent expedition, who established its true elevation of 6973 m, which has since been confirmed by SRTM data and modern high resolution Chinese topographic mapping. The subsidiary West Peak was climbed by a Finnish expedition in 2003 and a height of 6925 m was confirmed for Ulugh Muztagh II.

There have been only a few attempts to climb Ulugh Muztagh II and several of them have not even been able to reach the foot of the mountain. Getting near the mountain requires a difficult drive across largely unpassable terrain at the elevation of 4300-5000 metres. Expeditions who finally climbed the mountain spent 3 weeks on the approach alone using 4 or 6 wheel drive vehicles (http://en.wikipedia.org/wiki/Ulugh_Muztagh 4.11.2011). The measurements were made during this Finnish first ascent expedition in September 2003.

Island Peak (Imja Tse) is a 6189 m high mountain in the Himalayas of eastern Nepal, ten kilometres south from Mount Everest. The peak was named Island Peak in 1951 by Eric Shipton's party since it appears as an island in a sea of ice when viewed from Dingboche. The peak was later renamed in 1983 to Imja Tse, but Island Peak remains the popular choice. (http://www.nepalmountaineering. org/Imja Tse. 4.11.2011). Island Peak is one of the most popular trekking peaks given its difficulty (alpine PD+) and accessibility especially when supported by a Nepalese climbing guide. Coordinates are 27°55′21″N, 86°56′10″E. To climb Island Peak, the route follows the Everest base camp route up to the Pheriche at 4300 m and separates towards Dingboche. The base camp is situated at 5087 metres and High Camp is at around 5600 metres. The measurements were made during a Finnish expedition in November 2006.

Mount Everest (Chomolungma, Sagarmāthā) is the world's highest mountain, with a peak at 8848 m above sea level. It is located in the Mahalangur section of the Himalayas on the Nepal-China (Tibet) border. Coordinates are 27°59′17″N, 86°55′31″E. Mt. Everest has two main climbing routes, the southeast ridge from Nepal and the northeast ridge from Tibet, as well as many other less frequently climbed routes. The measurements were made during Finnish Everest expeditions in 2005 (the northeast ridge route) and 2009 (the southeast ridge route).

The ascent of the 2005 expedition to the base and advanced base camps were done first by car from Nepal via Kodar-Nyalam-Rongbuk Glacier, then setting up Base Camp at 5200 m on a gravel plain just below the glacier. To reach Camp II, climbers ascend the medial moraine of the east Rongbuk Glacier up to the base of Changtse at around 6100 m. Camp III (ABC – Advanced Base Camp) is situated below the North Col at 6500 m.

The ascent of the 2009 expedition to the Everest south side basecamp (EBC) was done via the normal EBC trekking route. Expeditions usually fly into Lukla (2860 m) from Kathmandu and pass through Namche Bazaar (3500 m). Climbers then hike to Base Camp via Pheriche (4300 m), where the route to Island Peak separates. It usually takes six to eight days, allowing for proper altitude acclimatization in order to prevent altitude sickness. Climbing equipment and supplies were carried by yaks and human porters to Base Camp on the Khumbu Glacier.

In Denali, Shisha Pangma, Ulugh Muztagh, and both Everest expedition, no porters were used. The climbers carried all their supplies above the base camps. Ascent profiles are presented in figure 1.

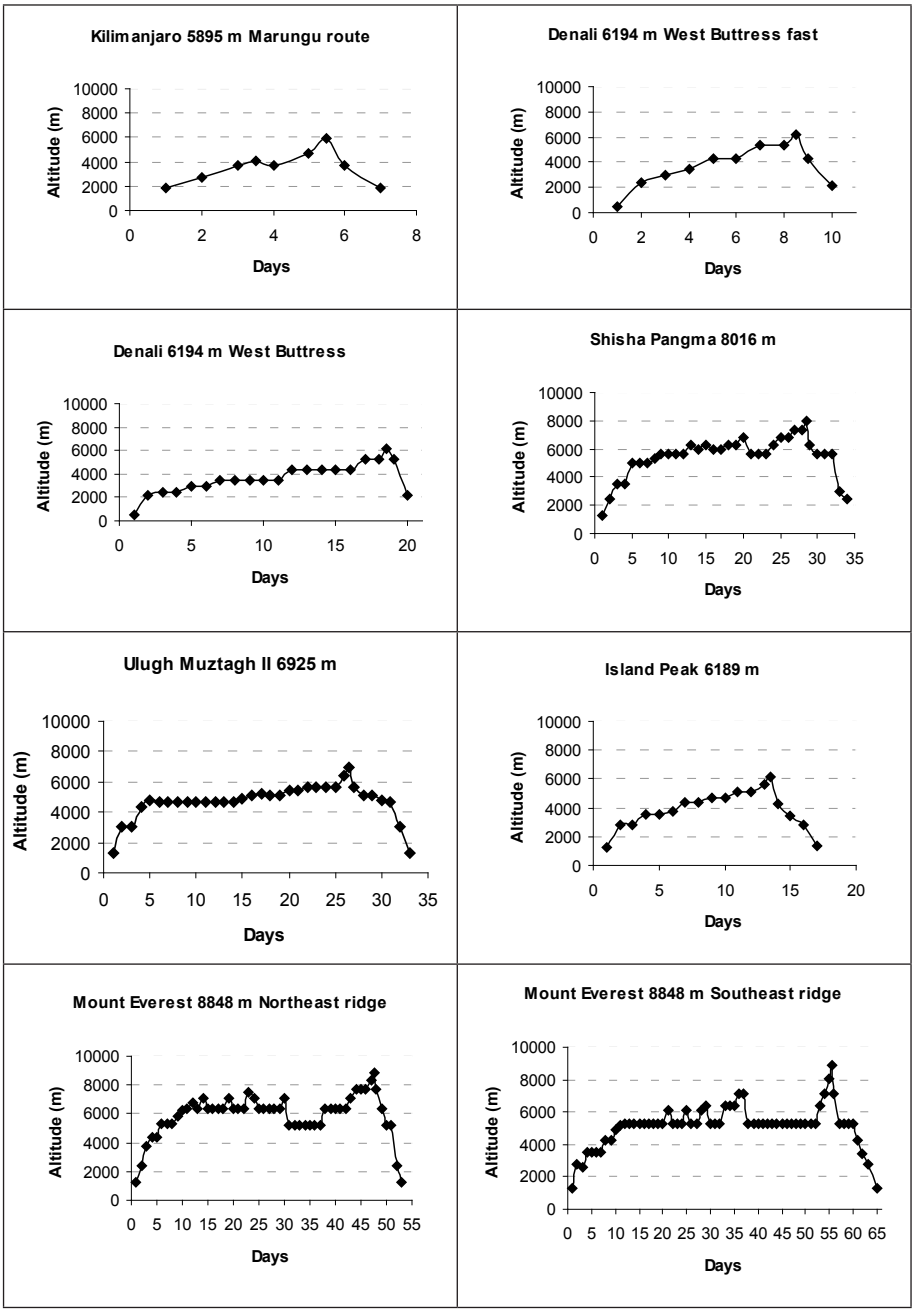


Figure 4. The typical ascent profiles of the mountains

2. SUBJECTS

The study groups consisted of participants of several different expeditions. A total of 186 different climbers were evaluated. Among them, 70 were females and 116 males. Study I was observational, to investigate the incidence of AMS experienced by Finnish travellers during their Kilimanjaro trek. A total of 130 participants from seven different trekking groups were asked to complete a Lake Louise self-report and clinical assessment score questionnaire on their way up Kilimanjaro, of which 112 were completed (study I) (Table 3). In study II, 83 ascents made by 74 different climbers were evaluated during their expeditions to Denali, Shisha Pangma, Ulugh Muztagh, Pheriche, Island Peak, and Mount Everest (Table 4). Some subjects in study III were also in study II; a total of 36 climbers from the expeditions to Denali, Shisha Pangma, and Mount Everest were evaluated (Table 5). The subjects for the case study (study IV) were from Shisha Pangma and Ulugh Muztagh expeditions.

2.1. FINNISH TREKKERS ON MOUNT KILIMANJARO (I)

Most of the Finnish Kilimanjaro trekkers were middle-aged or older people wishing to have an African experience, including a safari in the local national park and a climbing trek to Kilimanjaro. Most of them have no earlier climbing or high altitude experience and participated in a commercial trek via a Finnish tour operator during the winter season of 2006-2007. Information collected included demographic data, signs and symptoms experienced in the past 24 hours, earlier AMS, HACE or HAPE and experiences of altitudes over 3000 m (previous altitude experience, AE) or 5000 m (previous high altitude experience, HAE), use of medications (acetazolamide or others), the presence of chronic or other pulmonary disease, and smoking habits. In every group there was a Finnish guide trained in the management of high altitude illness and in the Lake Louise AMS scoring system (LLS). He was also trained to evaluate the signs and symptoms of AMS and he made the clinical assessment portion of the LLS. Each subject completed the questionnaire in camp every morning before continuing the trek and at Gillman's Point if they reached it (Table 3).

	Female (n=58)	Male (n=54)	Total (n=112)
Age, years (mean, range 16-74 yrs.)	50	52	51
BMI (mean)	23	25	24
Smokers (n)	4	8	12
Respiratory, cardiovascular and/or metabolic disease (n)	11	14	25
Acetazolamide 250 mg once a day (n)	8	2	10
No earlier altitude experience (n)	45	39	84
Earlier altitude experience (n)	11	8	19
Earlier high altitude experience (n)	2	7	9

Table 3. Demographic data (including gender, age, BMI, smoking habits, chronic diseases and use of acetazolamide) of the study I population

2.2. SPO_2 AND AMS (II)

Study II was concentrated on the evaluation of the predicative value of oxygen saturation measurements for AMS during ascent at altitudes of 2400-5300 m, which were considered critical altitudes for acclimatization during ascent. The study was conducted in 2001-2009 during eight expeditions to Denali (Denali 1, Denali 2), Shisha Pangma, Ulugh Muztagh, Pheriche, Island Peak and Mount Everest (Table 4).

A total of 83 ascents made by 74 (64 men, 10 women) different climbers were evaluated. Only healthy, non-smoking climbers participated in this survey. Their mean ± SD age during the ascents was 35 ± 9 yrs. and maximal oxygen uptake ($\dot{V}O_{2max}$) 54 ± 10 ml/kg/min (Table 4). None of the subjects had been exposed to an altitude above 1000 m within six months prior to this study. They were all lowland dwellers and recreational mountaineers, and during the expeditions none had taken acetazolamide as an AMS prophylaxis. Two climbers were taking regular medication for asthma but no one was using oral steroids, salmeterol, sildenafil, or nifedipine. All expeditions were organized in April-May. Ascent profiles were similar at sleeping altitudes but five expeditions had faster and three slower ascent rate. Before the expeditions, all members underwent a medical examination including resting 12-lead ECG and flow volume spirometry. To examine their exercise responses and to measure maximal oxygen uptake ($\dot{V}O_{2max}$), they performed an incremental clinical exercise test on a cycle ergometer (Ergoline 800S, Ergoline GmbH, Bitz, Germany). They started cycling at 20 W and work rate was increased stepwise 20 W/min up to volitional fatigue. A 12-lead ECG was obtained at rest before the exercise, and during the exercise test. All subjects had a normal ECG and none developed arrhythmias during the exercise test. During the exercise test, an alveolar gas exchange was measured breath-by-breath by a mass spectrometer (AMIS 2000, Innovision, Odense, Denmark) and a volume turbine (Triple V, Jaeger,

Mijnhardt, Bunnik, The Netherlands). Arterial saturation was recorded by pulse oximetry from the fingertip (Nonin 8600, Nonin Medical, Inc., Plymouth, MN, USA). The tests were performed mainly at the laboratory of the Foundation for Sports and Exercise Medicine / Department of Sports and Exercise Medicine, Institute of Clinical Medicine, University of Helsinki and partly at the Sports School of Finnish Defense Forces, Lahti.

Expedition	Total n	Female n	Age (Years)	$\dot{V}O_{2max}$ (ml $min^{-1} \cdot kg^{-1}$)	Mean ascent rate	Exposure to altitude
Denali 1	17	0	28 ± 4	64 ± 6	517 m/day	From 2200 m to 4300 m in four days, after 2 days rest, cont. 5300 m
Denali 2	14	2	33 ± 7	55 ± 7	258 m/day	Used nine days for the same route (5 days at 3500 m due to bad weather), 2 days rest at 4300 m, then cont. 5300 m
Shisha Pangma	6	0	30 ± 4	61 ± 3	500 m/day	From 2300 m to 5000 m in four days, 2 days rest, then cont. 5300 m
Ulugh Muztagh	10	1	35 ± 10	47 ± 5	660 m/day	From 1300 m to 4600 m in five days
Pheriche	7	0	36 ± 6	60 ± 4	600 m/day	From 1300 m to 4300 m in five days, two days back to 1300 m and then cont. after 5 days from 1300 to 5300 m in six days
Mt Everest	7	0	36 ± 6	60 ± 4	667 m/day	
Island Peak	15	7	47 ± 12	40 ± 7	278 m/day	From 2800 m to 5300 m in nine days
Mt Everest	7	0	38 ± 6	56 ± 4	278 m/day	From 2800 m to 5300 m in nine days
Total	83	10	35 ± 10	54 ± 10		

Table 4. Details of participants and ascent for each expedition (studies II-IV). Values for age and $\dot{V}O_{2max}$ are mean ±SD.

2.3. HRV AND AMS (III)

In study III, the prediction of AMS was sought by heart rate variation measurements during ascent at altitudes of 2400-6300 m. The study group consisted of participants of five different expeditions to Denali (Denali 1, Denali 2), Shisha Pangma, and Mount Everest (Everest 1, Everest 2). The expeditions were the same as in study II and subjects partly the same (Table 5). Thirty six different healthy volunteers (2 women and 34 men) with an age range from 24 to 45 years participated in this study. Subjects' mean age was 32 ± 6 years, body mass index (BMI) 25 ± 3 kg/m^2 and maximal oxygen uptake ($\dot{V}O_{2max}$) 59 ± 7 ml/kg/min.

Characteristic	no-AMS (n = 12)	AMS at some altitude (n = 24)	All (n = 36)
Age (years)(*	30 ± 5	33 ± 7	32 ± 6
BMI (kg/m^2)	24 ± 1	25 ± 4	25 ± 3
$\dot{V}O_{2max}$ (ml/kg/min)	60 ± 4	60 ± 9	59 ± 7

Values are mean ± SD. BMI = body mass index; $\dot{V}O_{2max}$ = maximal oxygen uptake.

Table 5. Demographic data (age, BMI and $\dot{V}O_{2max}$) of the study III population. There were no statistically significant differences in the basic characteristics between no-AMS and AMS groups.

2.4. TWO CASES OF AMS AND THEIR TREATMENT AT FIELD (IV)

Two different AMS patients and their successful treatment in the field are described, including the review of the current recommendations for prevention and treatment of AMS.

Case 1 is a 29-year-old healthy, non-smoking, and experienced Finnish mountaineer who participated in an expedition to a mountain over 8000 m high in Tibet. He had no previous history of AMS. He took four days to reach an altitude of 5000 m by car and spent three days there to acclimatize. After this period at 5000 m altitude, his resting heart rate (HR) was 60 per minute and the LLS showed no altitude related symptoms before getting ill at 5400 m. Case 2 is a 47-year-old, non-smoking, and experienced mountaineer, who, however, had not earlier been above 4000 m altitude, participated in a car drive in the highlands of Tibet. The road went to the highlands from 1300 m to a village at 2930 m, where he spent two nights to acclimatise. During the following day, the road rose to 4800 m and finally reached the Tibetan plateau at 5300 m altitude where altitude illness was diagnosed.

3. DATA COLLECTION DURING ASCENT (I-IV)

The ascent profiles during measurements at different expeditions are presented in Figure 5. The LLS data was collected every day at every camps and the summit of Mt Kilimanjaro (Study I) and SpO_2, HRV, and LLS data were collected every day during ascent at altitudes of 2400 m, 3000 m, 3500 m, 4300 m, 5000 m, and 5300 m in all expeditions (study II-IV), and up to 5600 m and 6300 m at Shisha Pangma (Study III-IV).

Oxygen saturation

Adaptation of the climbers to altitude was evaluated by measuring HR and SpO_2 at rest (R-SpO_2) and immediately after moderate exercise (Ex-SpO_2) during different phases of the ascent and combining these data with the Lake Louise Symptom Questionnaire (study II). HR was first measured in a sitting position, with HR monitors, after 15 min rest (Suunto T6, Vantaa, Finland; Polar S810, Kempele, Finland). Then R-SpO_2 was measured by finger oximetry (Nonin Medical, Onyx 9500, Plymouth MN, USA) while the subject was seated for an additional two minutes. During this period, R-SpO_2 was observed 4 times at 15 sec intervals and the average R-SpO_2 of these was recorded for data analysis. Ex-SpO_2 at altitude was measured with a standard walking test. The climber walked and controlled his speed with the HR monitor so that HR was approximately 150 beats / minute during 3-5 min walking. Temperature varied between + 20 to -15 °C and hands were covered by mittens during walking, which ended inside a tent. The inside temperature was mostly between + 5 and 20 °C because of extensive solar radiation or a stove. Immediately after the cessation of walking, SpO_2 was measured in sitting position by finger oximetry four times at 5 sec intervals during the first 15 s of recovery. The first value was recorded immediately when the subject stopped, the next one after 5 sec, the third after 10 sec and the last one after 15 sec. The average of these values was recorded as Ex-SpO_2 for data analysis. The main researcher took the measurements and AMS scoring by interviewing subjects and looking for the clinical signs. When the Denali 1 and Denali 2 groups were at different camps, a trained medical advisor took the measurements and AMS scoring. During all expeditions, HR, R-SpO_2, and Ex-SpO_2 were measured at altitudes of 2400 m, 3000 m, 3500 m, 4300 m, and 5300 m. Measurements were made in the morning after a night at that altitude. SpO_2 was observed to decrease after 15 seconds, but its measurement was attempted prior to its decline. During the first 15 sec, SpO_2 values did not change much, only a 0-1% unit, thus quite accurately reflecting SpO_2 during exercise.

Heart rate variation

In study III, HRV data (RR-intervals) collection was continued until the base camp of each mountain was reached. Measurements were performed every morning by heart rate monitor, after 7-8 hrs night rest, before doing anything else at that altitude (Suunto T6, Suunto, Vantaa, Finland or S810, Polar Electro, Kempele, Finland). HR recordings were made in the supine position, after at least 15 min of rest in the same position, while each subject lay quietly and breathed spontaneously. Then subjects started their HR monitors and continued lying down for three minutes. The last two minutes were chosen for data analysis. According to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force 1996), the preferred duration of ECG recordings for computing short-term HRV components is 5 minutes. The recording should last at least 10 times the wavelength of the lowest frequency bound of the investigated component (Task Force 1996). Thus a recording of approximately one minute is needed to assess the HF and approximately 2 minutes are needed to address the LF component. Autonomic cardiac function was assessed by analysis of R-R intervals (RRI). The duration of stationary RRI time series was 2 minutes, which should be adequate for the determination of the HRV components evaluated (Koskinen et al. 2009).

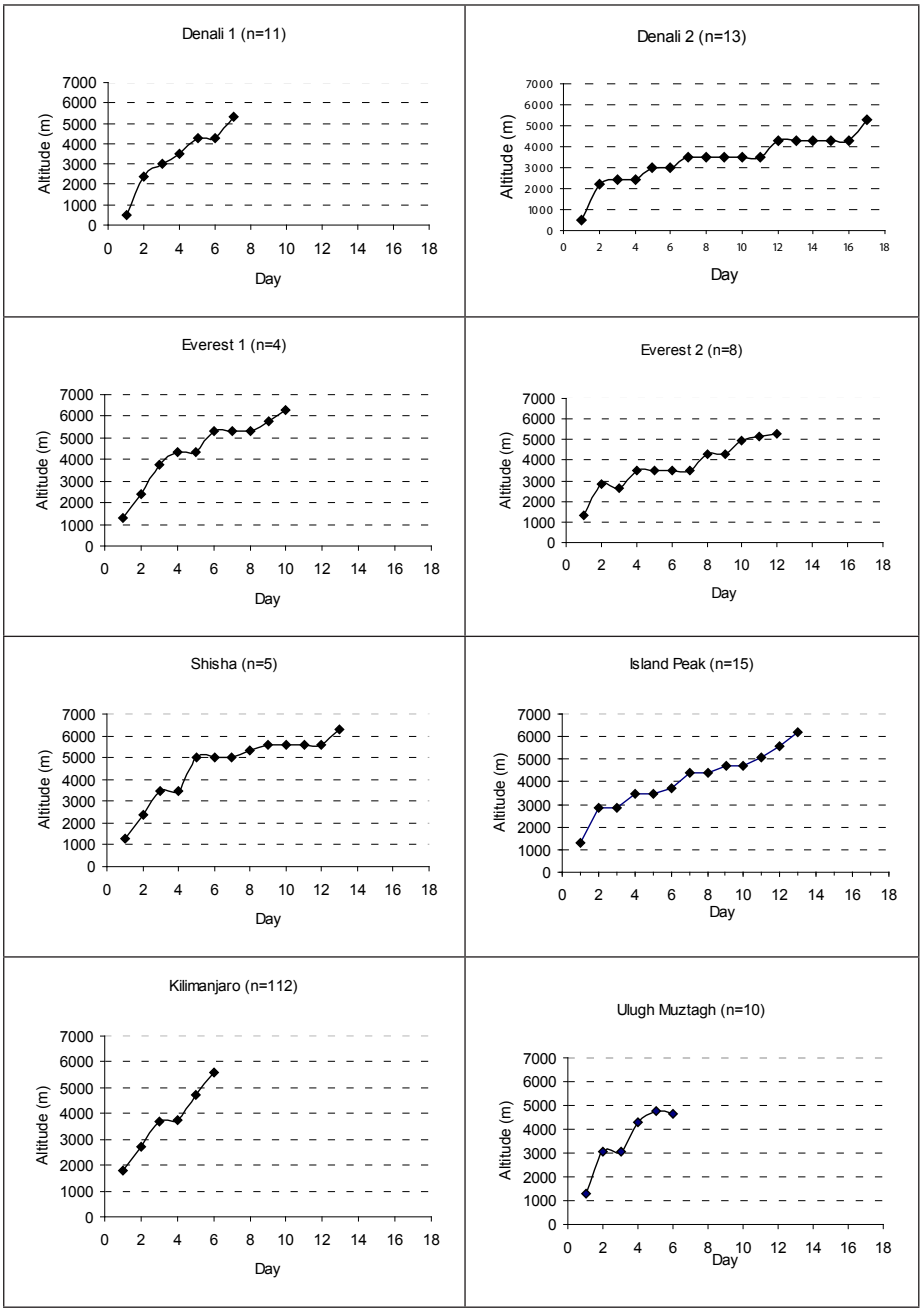


Figure 5. Ascent profiles during measurements at different expeditions.

After the HRV and SpO_2 measurements, subjects were scored according to the Lake Louise AMS scoring (LLS) system, which include a self-report questionnaire related to the presence and severity of symptoms and a clinical assessment (Hackett

and Oelz 1992). The LLS was obtained by adding the score of the clinical section to the self-report questionnaire. AMS was diagnosed according to a recent gain in altitude, the presence of headaches, and at least one of the following symptoms: gastrointestinal (GI) upset, fatigue, dizziness, or insomnia. To retrospectively study if HRV changes could have predicted AMS at higher altitudes, the study group was divided into two groups: 1) if the LLS was more than or equal to 3 at any altitude, the subject was assigned to the AMS group, and 2) if the LLS was 0-2 at every altitude measured, the subject was assigned to the no-AMS group.

Analysis of HRV data

Data processing and analysis were performed after the expeditions by Polar Precision Performance software (version 3.02.007) and Kubios software (version 2.0) (Niskanen et al. 2004). Areas of ectopy or artifact were identified and fixed by manual or automatic error correction. Segments containing ectopy or artifact more than 5% were excluded from the data analysis. Analysis of HRV was done for stationary 2-minute data segments. The power spectra were quantified by measuring the area in two frequency bands. The $HF_{2\,min}$ power was calculated for frequency band 0.15 – 0.40 Hz and $LF_{2\,min}$ power for frequency band 0.04 – 0.15 Hz.

4. STATISTICAL ANALYSIS (I-III)

Each data form was reviewed by the principal investigator for completeness. Differences in R- SpO_2, Ex-S SpO_2, and HR between AMS and non-AMS groups, as defined by Lake Louise AMS scores, were evaluated by t-test (I-II). Spearman's correlations between AMS and HR, R-SpO_2, and Ex-SpO_2 at different altitudes were calculated (II). Sensitivity, specificity, and positive and negative predictive values were calculated (II-III). The frequency of different HRV parameters was assessed by ^{2} tests with Yates' correction (III). Correlations between the LLS and clinical and autonomic variables were assessed by Pearson's correlation (III). In all tests, a p-value less than 0.05 was considered significant. Continuous values are presented as means ± standard deviation (SD). All analyses were done with SPSS 13.0 software for Windows (IBM, Chicago, IL, USA).

5. ETHICAL CONSIDERATIONS

All subjects were informed about the objective of the study and the experimental protocol both orally and by written information about the study. Written informed consents were obtained from the subjects prior to the measurements, as stipulated in the Declaration of Helsinki. Participation in the study was on a voluntary basis and possible participation did not affect the medical care of the climber unless the study revealed information that was of medical importance. The Ethics Review Committees of the University of Tampere and University of Helsinki, Finland, had approved the study protocol. The subjects were healthy volunteers and they were not paid to participate in the study. There were no invasive measurements. Cessation of the study took place at the request of the subjects.

RESULTS

1. THE PREVALENCE OF AMS ON MT KILIMANJARO (I)

In Study I, a total of 112 subjects (54 men, 58 women) completed the questionnaire at altitudes of 1700-3700 m, 107at 4700 m, and 38 at the summit. They were all low-land dwellers and recreational mountaineers. None had earlier diagnosis of AMS, HACE, or HAPE. The subjects ranged in age from 16 to 74 years, with an average age of 51 ± 10 SD (Table 3). Most trekkers were non-smokers, 9% had taken acetazolamide 250 mg daily as an acute mountain sickness prophylaxis and 22% were taking regular medication for respiratory, cardiovascular, and/or metabolic diseases. No one was using oral steroids, sildenafil, or nifedipine. The number of climbers at different altitudes and the presence of AMS are presented in Table 6. Climbers spent two nights at Horombo hut and no data is available regarding how many climbers still had AMS before resuming the ascent. Those reaching the summit were 35 men and 24 women. From the first time climbers 43/84 (51%) summitted. Only 8/19 (42%) of those trekkers who had earlier altitude experience, and 8/9 (88%) of those trekkers who had earlier high altitude experience, reached the summit. All those who had earlier high altitude experience, and 13/19 (71%) of those who had some altitude experience, climbed higher than Kibo hut. Those that reached the summit included: 11/15 receiving medication for chronic illness, 6/10 for asthma, and 5/10 using Diamox™.

The prevalence of AMS increased significantly with altitude ($p < 0.05$). The most common high altitude symptoms at 3700 m were sleeping difficulties, followed by headache and fatigue or weakness. At 4700 m, the most common symptoms were headache, fatigue or weakness, and sleeping difficulties. Only 6 subjects reported no signs and symptoms of AMS, HACE, or other high altitude related symptoms (HARS): 4 of them reached the summit and 2 turned back at 4700 m because of aching joints. Above Kibo Hut, and before reaching Gillman's Point, 17 trekkers had three or more LLS points. Of these, 7 reached the summit and 9 turned back. An equal distribution of scores was found between men and women. A total of 39 men and 45 women had AMS during their trek (75 %), 12 men and 8 women had HACE (18 %), and 12 men and 9 women had HARS (19 %). Twenty-two men and 17 women reached the summit in spite of AMS symptoms mostly at altitudes of 3700, but also at 4700 m (Table 6). Patients suffering from AMS included 12/15 receiving medication for chronic illness, 9/10 for asthma, and 8/10 using acetazolamide.

Proportion of climbers (n=112)												
Altitude (m)	Males (n=54) %	Females (n=58) %	Total (n=112) %	Going forward n	Turning down n	AMS		HACE		HARS		Cumulative percentage of AMS/HACE patients %
						n	%	n	%	n	%	
Mandara Hut 2743	100	100	100	112	0	10	9	0	0	6	5	9/0
Horombo Hut 3760	100	100	100	109	3 2 at 4000 m	39	35	7	6	14	13	38/6
Kibo Hut 4730	98	93	96	80	27	53	50	9	8	12	11	61/12
4700-5500	76	67	71	59	21	18	23	4	5	3	4	69/13
Gillman's Point or above	65	41	53			23	61	7	18	10	26	75/18

Table 6. The number of climbers at different altitudes and the presence of AMS

2. ARTERIAL O_2 SATURATION AND AMS (II)

In study II, a total of 84 ascents, made by 73 climbers were examined. No AMS (LLS ≥ 3) cases were recorded at altitudes of 2400 m or 3000 m. Prevalence of AMS at an altitude of 3500 m was 10% (8/83 subjects), at 4300 m 21% (17/83 subjects), and at 5300 m 37% (27/73 subjects). The total prevalence of AMS at altitudes 2400-5300 m was 47% (39/83 subjects) in the whole study group; 10 climbers had AMS at two altitudes and 2 at three altitudes. In detail, in the Denali 1 and 2 groups (AMS in 20/31 subjects), 3 climbers had moderate AMS (LLS 6-7), requiring assistance with descent and evacuation down (two subjects from 4300 m and one subject from 5300 m). In the Shisha group, 5 out 6 climbers suffered mild AMS (LLS 4-5), but they continued climbing after two days' rest. In the Ulugh group (AMS in 6/10 subjects), 5 had mild AMS and 1 had severe AMS with ataxia (LLS 8) at 5300 m. The subject with severe AMS had to be evacuated out with the assistance of a doctor. Trekking groups at Island Peak and Mount Everest Base Camp had 3 mild AMS cases at 4300 m and 7 at 5300 m (10/36 subjects).

Aerobic capacity, BMI, heart rate and arterial O_2 saturation responses

In study II, subjects with AMS had better aerobic capacity ($\dot{V}O_{2max}$ 58 ± 7 vs. 51 ± 11 ml/kg/min respectively, $p < 0.01$), and they were younger (32 ± 7 vs. 38 ± 11 yrs respectively, $p < 0.01$) than those in the non-AMS group. Four AMS subjects were obese (BMI > 30) and AMS was also associated with BMI and weight: BMI was 25 ± 4 and 23 ± 2 kg/m² ($p < 0.01$) and weight 77 ± 12 kg and 72 ± 7 kg ($p < 0.01$) in the AMS and non-AMS groups respectively.

Arterial O_2 saturation at rest and during exertion for climbers with no AMS and those experiencing AMS at that altitude are presented in Figure 6. AMS scores (LLS) at different altitudes and Spearman's correlation coefficients between HR, R-SpO_2, Ex-SpO_2, and AMS at different altitudes are presented in Table 7.

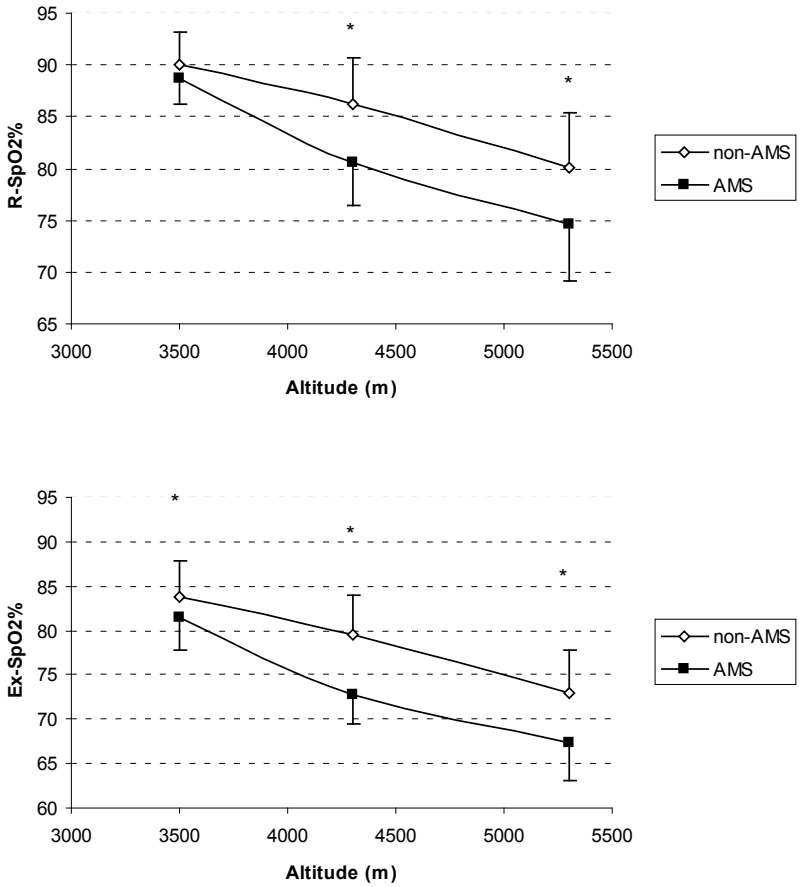


Figure 6. Oxygen saturation (mean, SD) at different altitudes at rest (above) and immediately after standard exercise (below) in AMS and non-AMS group. (AMS+ at 3500m n = 8, 4300 m n = 17, 5300 m n = 27, non-AMS at 3500 m n = 75, 4300 m n = 66, 5300 m n = 46. *Different from AMS, $p < 0.01$).

Altitude	Subjects/AMS cases	LLS	LLS in AMS cases	Correlation coefficients: LLS vs.		
				HR	R-SpO_2	Ex-SpO_2
3500 m	83/8	0.9 (0-5)	3.9 (3-5)	0.25 #	-0.03	-0.27 #
4300 m	83/17	1.6 (0-8)	4.3 (3-8)	0.30 *	-0.48 *	-0.62 *
5300 m	73/27	2.0 (0-8)	4.1 (3-8)	0.32 #	-0.48 *	-0.58 *

Table 7. Lake Louise Scores (LLS) at different altitudes (mean (range)) and Spearman's correlation coefficients of heart rate (HR), arterial oxygen saturation at rest (R-SpO_2) and immediately after exercise (Ex-SpO_2) versus LLS at different altitudes. #$p < 0.05$, *$p < 0.01$.

Prediction of AMS by arterial O_2 saturation and heart rate measurements

No AMS cases were recorded at the altitude of 3000 m or below. The climbers experiencing AMS at 3500 m (n = 8), had higher HR at rest at 3000 m altitude than the non-AMS group (n=75) (82 ± 11 vs. 74 ± 10, $p < 0.05$). However, at 3000 m, arterial O_2 saturation did not differ between the groups as R-SpO_2 was 91 ± 3 vs. 93 ± 3% and Ex-SpO_2 85 ± 3 vs. 86 ± 3% in AMS and non-AMS group respectively. As the ascent continued, the SpO_2 measurements became more predictive.

At 3500 m, the difference between subjects subsequently suffering AMS at 4300 m (n=17) and the non-AMS group (n=66) was obvious: both R-SpO_2 and Ex-SpO_2 were lower in subjects with AMS at 4300 m than in the non-AMS group (88 ± 2 vs. 91 ± 3, $p < 0.05$ and 80 ± 2 vs. 85 ± 4, $p < 0.01$ respectively), the difference in the Ex-SpO_2 between the AMS 4300 m and the non-AMS groups at 3500 m being 5% (95 % CI -1--4).

The subjects who subsequently developed AMS at 5300 m (n=27) had lower R-SpO_2 at an altitude of 4300 m than the non-AMS group (n=46) (82 ± 4 vs. 86 ± 5 respectively, $p < 0.01$). Ex-SpO_2 was also lower in the AMS group than in the non-AMS group (76 ± 4 vs. 79 ± 5 respectively, $p < 0.01$), the between-group difference in Ex-SpO_2 being 3% (95% CI -1--4) at 4300 m. Elevated resting HR at 3500 and 4300 m did not predict impending AMS at 4300 m and 5300 m (79 ± 10 vs. 73 ± 13, ns. and 77 ± 12 vs. 76 ± 12 respectively, ns.).

The potential of screening for AMS by measuring R-SpO_2 and Ex-SpO_2 is demonstrated by two examples in Table 8. In both examples, a different limit for SpO_2 is used causing changes in the predictive power of SpO_2 for subsequent AMS. First, the cut-off value for SpO_2 as a mean saturation at that altitude was chosen and subjects with AMS were compared to subjects without AMS at this altitude. The second cut-off value was chosen so that all climbers who subsequently developed AMS were identified. Specificity of Ex-SpO_2 was better than that of R- SpO_2 at 4300 m (Table 8).

SpO_2 (%)	AMS Score ≥ 3	AMS Score < 3	n	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %
R-SpO_2 at 4300 m (mean 85%)							
≤ 85	15	27	42	88	59	36	95
> 85	2	39	41				
n	17	66	83				
≤ 89	17	49	66	100	26	26	100
> 89	0	17	17				
n	17	66	83				
Ex-SpO_2 at 4300 m (mean 78%)							
≤ 78	15	14	29	88	73	52	95
> 78	2	38	40				
n	17	52	69				
≤ 79	17	24	41	100	52	41	100
> 79	0	28	28				
n	17	52	69				

Table 8. Two examples of the sensitivity, specificity and positive and negative predictive values of different measurements and different R-SpO_2 and Ex- SpO_2 levels at 4300 m. The first cut-off value is mean saturation of all climbers at that altitude and we have compared subjects with AMS at that altitude and subjects with no AMS. The second cut-off value is chosen so that all AMS patients are identified.

An average saturation level gave negative predicative values of 0.94, 0.95, and 0.59 in exercise tests at altitudes 3500 m, 4300 m, and 5300 m, respectively. In the same tests and altitudes, R-SpO_2 provided negative predicative values of 0.91, 0.95, and 0.66, respectively. R-SpO_2 and Ex-SpO_2, performed at different altitudes (3500-5300 m) to provide 100% sensitivity for the detection of AMS (i.e. in order not to miss any AMS patients before the onset of symptoms) are provided in Figure 7. The difference between R-SpO_2 and Ex-SpO_2, Δ SpO_2 at 3500 m for those subjects who suffered AMS was 7.4 ± 2.6 and those who did not suffer AMS 5.9 ± 3.4, ns., at 4300 m 7.8 ± 3.4 vs. 5.4 ± 3.1, $p < 0.01$ and at 5300 m 7.2 ± 2.7 vs. 7.1 ± 2.8, ns. respectively. Interestingly, Δ SpO_2 at 3500 m was also greater among subjects who suffered AMS at 4300 m than non-AMS subjects (7.7 ± 2.9 vs. 5.5 ± 3.3, $p < 0.01$) (Figure 8). At 3000 m vs. 3500 m and 4300 vs. 5300 m the difference was not statistically significant.

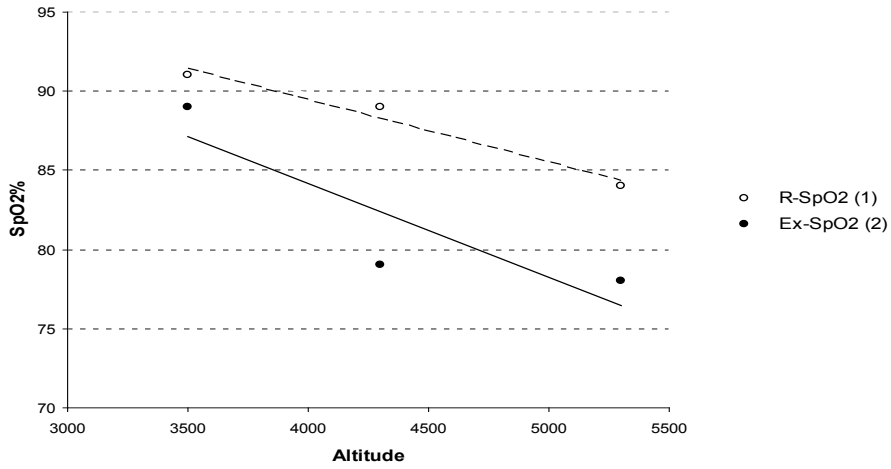


Figure 7. SpO_2 cut-off values giving 1.00 sensitivity for non-AMS for rest and exercise at different altitudes (3500 m, 4300 m and 5300 m). Lines for interpolating the cut-off values ("safelines") are also shown. So if the climber's measured SpO_2 is above the line, he will most probably not develop AMS during the ascent.

(1) Measurement based R-SpO_2 when sensitivity = 1.00 and "safeline"
(2) Measurement based Ex-SpO_2 when sensitivity = 1.00 and "safeline"

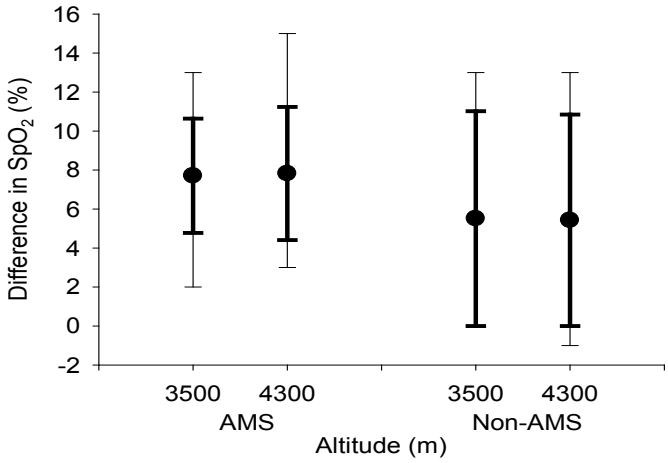


Figure 8. Desaturation (the difference between R-SpO_2 and Ex-SpO_2, Δ SpO_2) was stable at different altitudes among those climbers who did not get AMS (right). Those climbers who did not have AMS at 3500 m but later at 4300 m got AMS have higher mean Δ SpO_2 than those who did not get AMS (left) ($p < 0.01$). (Mean Δ SpO_2, SD and range).

3. HRV AND AMS (III)

In Study III, a total of 36 subjects were studied up to the altitude of 4300 m. Three discontinued because of AMS and the remaining 33 continued up to 5000 m and 5300 m altitudes. Five made all measurements at 5600 m and one at 6300 m altitude. The Denali 1 and Shisha expeditions reached the altitude of 5000 m in seven days (n=16) and the Denali 2 and Everest expeditions took 11-17 days to reach the same altitude (n=20) (Figure 5). Acute mountain sickness developed in 24 out of 36 (66%) subjects at some altitude between 3000 and 5600 m, including both women and 22 of 34 men, while twelve men (34%) did not get AMS at any altitude (no-AMS group). There were 11 AMS cases in the faster group and 13 AMS cases in the slower group. The groups showed no difference in age, BMI or $\dot{V}O_{2max}$.

Daily ascent rates recorded here were mostly higher than the recommendations (300 m/day), but quite common for these mountains (range 400-1500 m). In the no-AMS group, $RMSSD2_{min}$, $LF_{2\ min}$ and $HF_{2\ min}$ increased in the first few days of the ascent. All HRV parameters decreased above 3500 m while HR increased.

The numbers of the AMS cases at different altitudes are presented in Table 9. Among those who suffered from AMS, LLS scores varied between 3 and 8. Most of the AMS cases occurred at 5300 m (n = 10), and the prevalence of AMS increased significantly with altitude and fast ascent rate on the day before the onset of AMS (both $p < 0.001$) (Figure 5). Headache and difficulty in sleeping were the most frequent symptoms of AMS followed by GI symptoms, fatigue, and dizziness.

At 2400 m altitude, $RMSSD_{2\ min}$ and $HF_{2\ min}$ were lower and HR higher among those climbers who got AMS at lower altitudes (3000-4300 m) (n=12) than in those who got AMS 3-7 days later at higher altitude (≥ 5000 m) (n=12) or not at all (n=12) (Table 9). Heart rate, $lnHF_{2\ min}$ and $RMSSD_{2\ min}$ at 2400 m correlated with the lowest altitude at which a climber suffered AMS (AMS altitude) (Figure 8). There were no differences between R-SpO_2 at 2400 m and later onset of AMS, but Ex-SpO_2 was statistically higher in the no-AMS than the AMS group at 3000-4300 m ($p < 0.01$) (95% CI 3 (1-5) and in the AMS at ≥ 5000 m group ($p < 0.05$). However, Ex-SpO_2 did not correlate with the AMS altitude ($r=-0.028$). At the altitude of 2400 m $RMSSD_{2\ min} \leq 30$ ms and Ex-$SpO_2 \leq 91\%$ all had 92% sensitivity for AMS at 3000-4300 m if ascent continued without extra acclimatization days (Figure 9). The sensitivity, specificity, positive and negative predicative values for chosen cut-off values are presented in Table 10.

	no-AMS (n=12)	AMS at 3000-4300 m (n=12)	AMS at ≥ 5000 m (n=12)
HR (beats/min)	70 ± 9	82 ± 15*	62 ± 8*†
RMSSD (ms)	43 ± 25	21 ± 13*	48 ± 32†
lnLF (ms^2)	7.3 ± 0.9	5.7 ± 1.1‡	6.4 ± 0.9
lnHF (ms^2)	6.1 ± 1.1	4.5 ± 1.9*	6.6 ± 1.7†
LF/HF	4.9 ± 4	6.2 ± 6	1.2 ± 1.1‡†
R-SpO_2	94 ± 1	93 ± 2	94 ± 2
Ex-SpO_2	91 ± 2	88 ± 3‡	89 ± 3*

Values are presented in mean ± SD. (*p < 0.05, †p < 0.01, difference between AMS 3500-4300 m vs. no-AMS groups and AMS ≥ 5000 m vs. no-AMS groups, †p < 0.05, difference between AMS 3500-4300 m vs. AMS ≥ 5000 m).

Table 9. Resting heart rate (HR) and HRV parameters at 2400 m among the climbers who subsequently developed acute mountain sickness (AMS) at two different altitude ranges, and those who had no subsequent AMS.

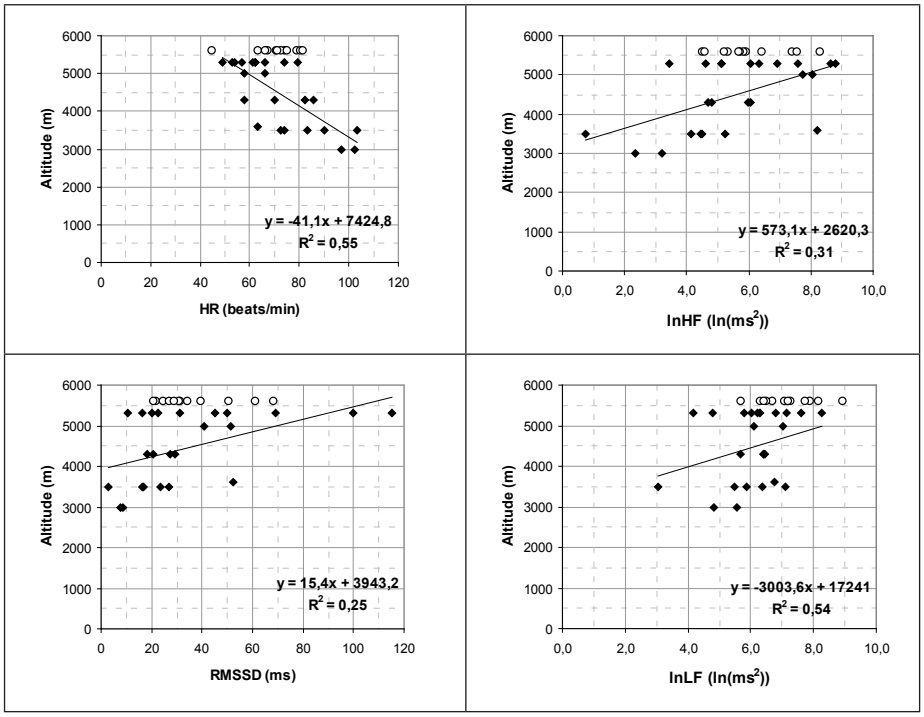


Figure 9. Negative correlation between HR and positive correlation between lnHF, lnLF, and RMSSD at 2400 m altitude and the lowest altitude at which a climber got AMS (HR r = -0.743, p < 0.01; lnHF r=0.558, p < 0.05, lnLF r=0.302, p < 0.05, RMSSD r=0.495, p < 0.05). No-AMS subjects' datapoints are added at 5600 m level (symbol ○).

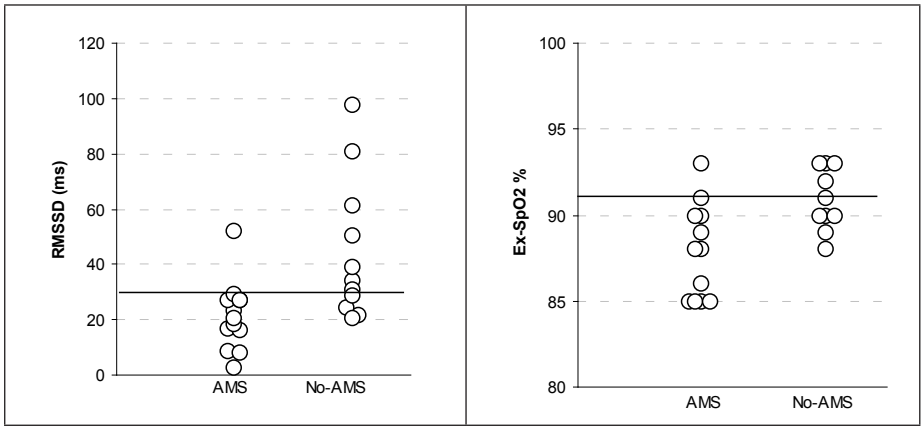


Figure 10. Scattergram showing the distribution of values of RMSSD and Ex-SpO_2 measured in 24 study subjects at 2400 m in AMS and no-AMS. The cut-off lines $RMSSD_{2\ min} \leq 30$ ms and Ex-$SpO_2 \leq$ 91% are for 92% sensitivity for AMS.

	Sensitivity	Specificity	Positive predicative value	Negative predicative value	95% Confidence Interval
$RMSSD_{2\ min} \leq 30$	92%	58%	61%	83%	22(5-39)
Ex-$SpO_2 \leq$ 91%	92%	40%	65%	80%	3(1-5)

Table 10. Sensitivity and specificity of chosen parameters at 2400 m altitude for AMS at 3000-4300 m.

4. CASE STUDY (IV)

Two climbers developed a severe AMS due to too rapid ascent and their denial of the symptoms. In the first case the patient first showed symptoms of AMS at 3000 m altitude. The patient did not tell anyone about his symptoms. During the following day, the expedition continued ascend to 4800 m and the patient's headache symptoms increased. Because of the headache, he started to take paracetamol (500 mg three times a day) as pain medication. When the doctor of the expedition talked to him, he reported that he was well and had no symptoms of AMS at all. Next day at 5300 m the symptoms were so clear that he could not deny them. He had a severe headache, faintness, and moderately strong light-headedness which impaired his co-ordination and caused ataxia. His sleep the previous night had been extremely fragmented and he had slept only a few hours. SpO_2 was 58% at rest, there were crackles and bubbling in the lung auscultation, HR was 110/min, and LLS was 6 and later it was 8. At this moment, AMS, HAPE and HACE were diagnosed and the following treatment was initiated: 250 mg of acetazolamide, 20 mg of nifedipine

and 8 mg of dexamethasone once, and then 4 mg every eight hours. Because of restricted oxygen capacity, oxygen was given to him at intervals of a couple of hours for 20 min as adjuvant care 4 l/min. The patient's urgent evacuation was necessary but since the vehicles had broken down, the evacuation was delayed. Finally he was transported two days later by car from 5300 m to 1500 m where the breathing problems resolved quickly. He still had minor ataxia and light-headedness and he was unable to continue the expedition. Four weeks later, the patient was totally symptom-free and healthy.

In the second case, the climber hiked with a rucksack after 3 days acclimatization period from 5000 m to 5400 m altitude where the symptoms started and AMS developed quickly. There was a 400 m ascent to the next camp, and the distance to be covered was 15 km. The weather was first sunny and warm, later it was cloudy, and at times there was a slight snowfall. The climber drank 1900 ml of fluid during the trek. During the day, he excreted 500 ml of urine. On arrival at the campsite, at the height of 5425 m, he was accompanied by one fellow climber. He felt a little tired with a slightly slowed coordination, but the camp routines went fast. After putting up the tent, he felt very tired and shivering cold. In the sleeping bag, his body temperature under the arm rose to 37.8°C. He consumed fluids in the form of food and drink in total 2400 ml.

During the following night, he did not urinate at all. On falling asleep at 8:00 p.m. his HR was 120/min and respiratory rate 30/min. After he fell asleep, his companion soon perceived periodic breathing caused by high altitude which is similar to Cheyne-Stokes type breathing, and at 10:00 p.m., his HR rose to 130/min. Furthermore, the shortness of breath and the feeling of compression were found in the chest. The breathing sounds were bubbling when auscultated. The SpO_2 was 59%, LLS 8 and AMS and HAPE were diagnosed. 250 mg of Asetatzolamide and 20 mg of nifedipine began to be administered every eight hours and the development of the situation was monitored during the night at intervals of 1–2 hours. The subject drank 600 ml of water during the night. When the symptoms eased at 2:00 a.m., with RR 21/min and HR 115/min, he was given permission to sleep in spite of a slight headache. In the morning, he was feeling well, except for slight faintness and headache. He excreted 750 ml of urine, his RR was 20/min, SpO_2 71% and HR 105/min. At lung auscultation no sounds of oedema were heard at any stage. 8 points on the LLS scale indicated moderate mountain sickness and the patient should have been treated with descent, oxygen or a portable hyperbaric chamber. At this camp, they had no oxygen treatment or evacuation facilities. They communicated via satphone with their travel clinic. According to the doctor's instructions, he stayed at this altitude because descent was not possible. After two days' rest, all symptoms disappeared, SpO_2 was 74%, HR 95/min and he continued four kilometers on to the next camp, which was 200 m higher and had better facilities. The ascent went without problems and no further symptoms of AMS or HAPE occurred. The

medication was discontinued after three nights without any problems in a 5650 m camp when his HR was 75/min, RR 18/min and SpO_2 85%. After this, the subject participated in the expedition normally without any restrictions.

DISCUSSION

1. OVERVIEW

The purpose of this study was to assess the prevalence of AMS at Kilimanjaro, to investigate the roles of Ex-SpO_2, R-SpO_2, and HRV in predicting AMS during the expeditions, and to describe the problems of recognizing and treating AMS in the field.

The most important finding in study I was that the incidence of AMS is high in trekkers ascending Mount Kilimanjaro. Some of the contributing factors are preventable, so we recommend an educational programme for all of the trekking agencies who guide on this peak and, in particular, the Tanzania-based guiding agencies which are typically driving these very fast ascent rates.

The most important finding of study II was that climbers who maintain their oxygen saturation at rest, and especially with exercise, most likely do not develop AMS. The results suggest that daily evaluation of SpO_2 during ascent immediately after exertion is more indicative for a good level of acclimatization than R-SpO_2 alone or changes in resting HR. Ex-SpO_2 testing can be quite easily standardized, even in extreme field conditions, and may prove valuable in the diagnosis and avoidance of AMS; however, further development of this method is required. We recommend that expeditions take R-SpO_2 and Ex-SpO_2 measurements every day to distinguish those who are acclimatizing well and those who may have problems later. Once climbers have been identified as being at risk, they can be advised by the leaders of teams or expeditions to take additional time to acclimatize. This method may enable the leaders of teams and expeditions to optimize their ascent rates and avoid interruptions in operations, which might otherwise be necessary in order to enable the rescue of climbers afflicted by altitude sickness. The safeline demonstrated in figure 7 needs to be tested on larger groups for different expeditions and altitudes in the field.

Oxygen delivery is dependent on cardiac output and CaO_2. Within 24 hours after ascending to new altitude, cardiac output and HR are increased due to the hypoxia-induced increases in sympathetic nerve activity. This increase in sympathetic nerve activity remains persistent even in well-acclimatized subjects (Palmer 2010). Heart rate and cardiac output tend to fall over several days after arrival to a new elevation. The decline in heart rate is of a variable degree and has been attributed to increased vagal input and to downregulation in the number of β-adrenergic receptors (Palmer 2010). In study III, the elevated HR also predicts AMS in 3-5 days, and very low

HR at the 2400 m altitude was associated with a later onset of AMS. The HRV parameters had slightly better statistical power to predict AMS in the near future but the method for its measurement is more complex than for HR.

As a conclusion from study III, at 2400 m decreased $RMSSD_{2\ min}$, $lnLF_{2\ min}$ and $lnHF_{2\ min}$ predicted AMS in a few days if the ascent continued without rest days. Autonomic cardiac response to increasing altitude could be a low-cost non-invasive test to predict impending AMS and to help distinguish those who are at risk for AMS and those who are acclimatizing well. The trigger values typical for impending AMS await further studies.

In conclusion from study IV, we can say that prevention is the safest and the most efficient method in the care of AMS. The symptoms may not be easily noticed, and thus curative measures may be delayed. Remedying the situation requires radical actions such as interrupting the ascent, descending, patient evacuation etc. The possibilities for medical treatment are limited and a portable pressure chamber and administering additional oxygen bring only temporary relief. Realizing the risk of AMS, making realistic and safe ascent plans, active elicitation of symptoms and timely reaction to them, in other words, discontinuing the ascent or descending, help to reduce and even to prevent the development of serious problems.

2. INCIDENCE OF AMS (I)

The rate of ascent is a big issue on Kilimanjaro, where several guiding agencies go from base to summit and back in only 6 days (Karinen et al. 2009). Despite the large number of studies on AMS incidence in Nepal and other areas, and despite the large numbers of people climbing Kilimanjaro each year, little has been published about AMS incidence on Kilimanjaro (McIntosh and Prescott 1986, Moore et al. 2001). The fast ascent rates and very high incidence of AMS are typical for this mountain. In study I, the prevalence and severity of AMS was assessed in a representative population of 112 Finnish trekkers during a climb on Mount Kilimanjaro, Tanzania. Interestingly, as high as 75% incidence of AMS was found in Kilimanjaro trekkers at Marungu Route. We consider this as a representative of groups commonly trekking on this peak. Although we expected a high proportion of subjects to have one or two high altitude related symptoms, the prevalence of AMS was surprisingly high. The ascent rate at Marungu Route was faster than current recommendations suggest (Hackett and Roach 2001, Basnyat and Murdoch 2003).

In spite of the fact that AMS, HAPE, or HACE may cause fatal symptoms, it is noteworthy that so many people seem to push on to the summit despite having the symptoms of AMS. Even though 42 (38%) subjects suffered from the symptoms of AMS at 2700 or 3700 m, none of them turned back. Instead, they rested a day at Horombo Hut and continued to climb after that. It is possible that their symptoms

had gone away by the time the group was ready to ascend the next morning. We do not have data how many of them still had AMS before continuing the ascent. Only three trekkers turned back from Horombo Hut, two because of high blood pressure and one because of mental problems (depression and loss of motivation). Twenty-nine (17 men and 12 women, 36%) trekkers continued the ascent to 4700 m even though they had AMS. Twelve of them gave up the ascent before the summit (8 men and 4 women). Many of the climbers had AMS in at least two different camps, some even more often and they should have abandoned the ascent earlier (Table 6). Among the Gosainkund pilgrims in the Nepal Himalayas at 4300 m, the incidence of HACE has been 31% (Basnyat et al 2000b). Ataxia has been mentioned as an early sign of impending HACE and its incidence at 4505 - 4779 m is 0.26% (Wu et al 2006). In study I, based on the presence of ataxia, headache, and changes in mental status, 6% had HACE at 3700 m, 8% at 4700 m, and 18% at 5700 m (table 6). Two climbers had mentioned the ataxia symptom at least two camps, or a day, before turning down at 5000 m, two have had the ataxia symptom at three camps, and two had a moderate AMS and HACE at 4700 m (LLS 7 points including moderate ataxia) before reaching the summit. So, they were still continuing ascent even though it would have been essential for them to abort the ascent immediately. This means that they were willing to take the greater risk of serious AMS or they did not know enough about altitude sickness and the risks of high altitude travel.

The different ascent rate between Kilimanjaro, and Mount Damavand and Annapurna area trekkers may be one reason for the different incidences of AMS. The Marungu Route is an extremely fast ascent to a very high altitude. This is the most obvious reason why the incidence rate is so high in Kilimanjaro trekkers. The incidence rate of AMS might be lower on other routes such as the Machame Route, which uses a slower ascent rate but no data was collected on this route. In this study population, ten climbers used acetazolamide 250 mg daily for prophylaxis. Eight of them got AMS. There has been a lot of discussion about the dose of acetazolamide in prophylactic use (Basnyat et al. 2006). Even people who took acetazolamide had a relatively high incidence of AMS. This suggests that even on prophylaxis, too rapid an ascent will cause sickness.

There were no differences in the incidence of AMS based on age or gender, a finding which agrees with that of previous studies (Honigman et al. 1993). Women seemed to descend earlier than men if they had HARS/AMS symptoms. We concur with the literature that the incidence of AMS increases with altitude. Similar to earlier reports, an abrupt increase in incidence at altitudes over 4700 m was found here (Maggiorini et al. 1990, Gaillard et al.2004, Ziaee et al. 2003).

Overall, the study population was comprised of mostly healthy subjects spending their leisure time or holiday in Africa and eager for a high altitude experience at the highest point of Africa. Ninety-two percent of them were normal travellers or hikers with no earlier experience of high altitudes or mountain climbing. This

population can be considered a representative cohort of the trekkers on Kilimanjaro because 86% completed the questionnaire. As subjects with the symptoms of AMS presumably tend to participate in medical studies more eagerly than those without, this may lead to a slight overestimation of the prevalence of AMS. On the other hand, we had four climbers who reached the summit with no altitude related symptoms. Two of them were men, aged 50 and 56 years and one woman aged 42 years. There may have been some underestimation of symptoms because it was their first trek at high altitude or because of group dynamics. One 56 year-old woman had some earlier altitude experiences and she reported no symptoms at all during this or earlier treks reaching 4000-5000 m.

Normally, the Kilimanjaro treks have a fixed timetable and for commercial reasons there is little opportunity to spend any extra days for acclimatisation in any camps. The current recommendations are to ascend only 300-600 m per day and to spend an acclimatization day for every 600-1200 m altitude gain (Hackett and Roach 2001, Basnyat and Murdoch 2003). Normal ascent rates on the Marungu Route are 900 m on the first day and 1080 m on the second day. On the third day trekkers usually rest or do a daytrip to an area 300 m higher then return to Horombo Hut to overnight. On the fourth day, the ascent is 940 m before the attempt on the summit, which is on the fifth day and the ascent rate is 970 m to Gillman's Point or 1180 m to Uhuru Peak (Figure 4). The main reason for the high incidence of AMS in Kilimanjaro seems to be rapid ascent.

It is conceivable that young hikers or males overdo things more readily and ignore the warning symptoms of AMS, and hence are at risk of developing a full-blown AMS syndrome. There is evidence to suggest that certain pulmonary vascular abnormalities predispose to HAPE but not to AMS (Luks and Swenson 2007). Underlying health conditions, such as heart disease, diabetes, and hypertension, do not predispose to AMS (Honigman et al. 1993). In study I, there was no significant difference between smoking, use of acetatzolamide, the history of chronic diseases or asthma and others in reaching the summit or having more than 3 LLS points.

Trekkers usually have experienced guides and several well-acclimatized porters with them and there are no technical problems on the Marungu Route. It is easy to send back trekkers with AMS with the assistance of 1-2 porters. So far there have been no fatalities due to AMS among Finnish trekkers on Kilimanjaro, but the situation may change when older and greater number of trekkers want to try this challenge. Still, there have been numerous fatalities on this mountain among different nationalities indicating the need for proper education and evaluation of trekkers and clear instructions if AMS emerges.

3. PREDICTION OF AMS BY SPO_2 AND HRV MEASUREMENTS (II-III)

The diagnosis of AMS is clinical, but there are changes in physiological parameters before the onset of AMS. SpO_2 at rest and during exercise at lower altitude were predictive of subsequent AMS at higher altitude when the ascent continued. Subjects susceptible to AMS had lower HRV before the clinical manifestations of AMS than those who acclimatized well and did not get AMS. This is a new finding and offers fascinating options for predicting AMS at high altitude in field conditions.

3.1. ARTERIAL O_2 SATURATION (II)

Although R-SpO_2 was of some use in distinguishing AMS patients from the non-AMS group at 3500-5300 m, Ex-SpO_2 was found to be a slightly better method than R-SpO_2 to predict impending AMS at every altitude between 2400 m and 5300 m. Hypoxia elicits neurohumoral and hemodynamic responses in both the brain and lungs, resulting in overperfusion of microvascular beds, elevated hydrostatic capillary pressure, capillary leakage, and consequent oedema (Hackett and Roach 2001). On the other hand, hypoxia, exercise, and cold environment have been shown to increase vasoconstriction in pulmonary circulation (Gallagher and Hackett 2004). Individuals with acute altitude sickness hypoventilate (Moore et al. 1986), their sympathetic activation is elevated (Mazzeo et al. 1995), and ventilatory drive in response to hypoxia is reduced (Barry and Pollard 2003). At sea level, both an excessive alveolar-to-arterial PO_2 difference (A-a DO_2) (> 25 to 30 torr) and inadequate compensatory hyperventilation (arterial PCO_2 > 35 torr) commonly contribute to exercise-induced arterial hypoxemia, as do acid- and temperature-induced shifts in O_2 dissociation at any given arterial PO_2. In turn, expiratory flow limitation may present a significant mechanical constraint to exercise hyperpnoea, whereas ventilation–perfusion ratio maldistribution and diffusion limitation contribute about equally to the excessive A-a DO_2 (Dempsey and Wagner 1999). At high altitude, the hypoxemia among subjects with AMS is primarily due to an anatomical shunt and/or diffusion impairment and ventilation–perfusion mismatch (Loeppky et al. 2008). An additional factor that may possibly affect SpO_2 at high altitude is extra vascular lung water accumulation and/or inflammatory changes in the peripheral airways (Bärtsch et al. 2002). The measurement of the SpO_2 value after light exercise has been shown to be a convenient means of estimating the level of high altitude acclimatization among healthy subjects (Saito et al. 1995), and the degree of hypoxemia during exercise has been shown to correlate with the subsequent development of AMS at 4300 m altitude (Staab et al. 2006).

In this study, no AMS patients were evident before 3500 m altitude, but climbers that experienced AMS later at higher altitudes had significantly lower SpO_2 values at lower altitudes than climbers not developing AMS. For example, Ex-SpO_2 was lower at 3500 m in the AMS 4300 m group than in the non-AMS group ($p < 0.01$). Thus, with Ex-SpO_2 measurements, the first signs of impending AMS could be seen before any other symptoms at 3500 m in the group that developed AMS at 4300 m (Figure 8).

In study II, a correlation was seen between SpO_2 and AMS. The correlation was significantly higher between Ex-SpO_2 and AMS than R-SpO_2 or HR and AMS at every altitude examined (Table 7). There was also a weak association between R-SpO_2 and a strong association between Ex-SpO_2 and subsequent development of AMS. Monitoring SpO_2 during exercise in addition to rest seems to improve the prediction of impending AMS, especially at moderate altitude (3000-3500 m). The predictive power of Ex-SpO_2 was also seen at high altitude (4300-5300 m) but the difference between Ex-SpO_2 and R-SpO_2 was smaller. Desaturation level during exercise had some predictive power at 4300 m but not at any of the other altitudes examined.

Expeditions or individual climbers may ascend faster than the recommendations due to the conditions of the route or climate. In study II, a method was sought for mountaineering expeditions to use saturation measurements at different altitudes to predict AMS if the ascent continues without extra acclimatization days. There was considerable variation in saturation levels where some climbers developed AMS and some did not at a given altitude. If an estimated safe saturation level at different altitudes is desired, the specificity of the mean saturation of the non-AMS group is not optimal. Because the variation between saturation levels is quite large, it is difficult to estimate a 100% safe saturation level and too many climbers will be classified to the AMS risk group (see Table 8). Thus, at saturation levels where sensitivity to AMS is 100%, the number of those who are declared to be at risk but do not subsequently develop AMS is too high. This type of ("safeline") approach provides an estimate of a safe saturation level during a 3500-5300 m expedition, which can help to identify a population that does well at altitude from those who may need an extra acclimatization day. Furthermore, at high altitude, the consequences of false positives are still minor. Those whose saturation levels are the lowest could be monitored more intensively or an extra acclimatization day could be recommended. On the other hand, approximately equal numbers of false positives and correct predictions were seen here when taking the mean Ex-SpO_2 value as a cut-off at 4300 m (see Table 8). This finding has practical consequences with regard to the proper planning of the ascent. Given their strong association with Lake Louise scores (Table 7), man can speculate that post-exercise desaturation measurements have an additive value to R-SpO_2 and they all (R-SpO_2, Ex SpO_2, Δ SpO_2) represent the changing level of acclimatization and impending AMS.

3.2. HEART RATE VARIATION (III)

In study III, a correlation was found between HRV at 2400 m and the later onset of AMS. The diagnosis of AMS is clinical, but some specific changes in cardiac autonomic function measured by HRV have been estimated to be more sensitive in the detection of the early signs of AMS than clinical symptoms alone at high altitudes (Saito et al. 2005). HRV is reported to decrease in absolute units (Kanai et al. 2001, Bernardi et al. 1998, Hughson et al. 1994) and LF/HF mostly increased when subjects got AMS (Loeppky et al. 2003, Lanfranchi et al. 2005, Chen et al. 2008, Huang et al 2010). There are also, however, opposite findings reported about HRV (Koehle et al. 2010). Studies conducted in the field at high and extreme altitudes (> 5000 m) are still lacking.

During mild sympathetic activation, an observed increase in HR has been reported to be associated with an increase in LF power (Elghozi and Julien 2007). With more intense sympathetic stimulation, the increase in HR was associated with an overall decrease in HRV, including its LF component (Antila 1979, Elghozi and Julien 2007). Our present findings on changes in HRV values at extremely high altitudes support this concept.

At 2400 m, the no-AMS group had higher HRV and lower $HR_{2\ min}$ than the AMS group. The differences are not related to differences in physical fitness in the AMS and no-AMS groups because the basic maximum oxygen uptake did not differ significantly between the groups (59 ± 11 vs. 60 ± 4, $p > 0.05$). Furthermore, clear changes were not associated with the ascent. However, in the no-AMS group $HF_{2\ min}$ tended to be lower, while $LF_{2\ min}$ tended to be higher than in the AMS group. The physiological significance of these findings remains uncertain but they do not directly support the earlier assumption that AMS is simply connected with higher cardiac sympathetic activity. Rather, it seems that a rise in cardiac sympathetic activity would have been a protective phenomenon against altitude illness. However, altitude illness is a dynamic process. It may be that as the AMS proceeds, HRV could further decrease. In other words, changes in HRV were related to higher altitudes in all climbers, but also notably to acclimatization and especially to failure to acclimatize.

The present findings are still generally in agreement with those of earlier studies and provide further insights on the usefulness of HRV in the prediction of AMS under field conditions. Several studies have shown that SpO_2 measurements at rest (R-SpO_2) and immediately after exercise (Ex-SpO_2) are predictors of AMS (Saito et al. 2005, Roach et al. 1998, Burtscher et al. 2008). Our study supports this. At 2400 m altitude the Ex-SpO_2 was statistically higher in the no-AMS group than AMS 3000-4300 group ($p < 0.01$) and AMS ≥ 5000 m group ($p < 0.05$). However, the SpO_2 measurements made by pulse oximetry in field conditions are susceptible to many disruptive factors (for example temperature, bright light, cold fingers etc.) (Luks and Swenson 2011). Therefore, it is desirable to have another parameter(s)

to follow-up for AMS susceptibility. Our findings support the possibility that HRV could be used along with commonly measured physiological parameters, HR and SpO_2, clinical status, and Lake Louise questionnaire for AMS prediction, in the short time period at moderate altitudes. The altitude of 5000 m was reached mainly 1-2 weeks after the measurements at 2400 m and the ascent rates per day were high just before reaching this altitude (700-1500 m/d). This may explain better the high prevalence of AMS at 5000-5300 m than a predominant vagal modulation at rest at 2400 m.

4. TREATMENT OF AMS IN THE FIELD (IV)

Normally, lowland dwellers make their first ascents to high altitude via the easiest or most popular ways by using commercial tour operators. In the Himalayas, trekkers may take 10-15 days to reach about 5000-6000 m. The ascent of Kilimanjaro (5984 m) usually takes five or six days. Some international airports like Lhasa or La Paz are even situated 3650-4058 m above sea level. Most of the tour operators have experienced guides with them but, for example, the business travellers may travel alone. It is important for all doctors and nurses who are giving health advice to travellers to have a basic knowledge of AMS. Patients may ask advice when planning a trip to highlands or mountains, or health care professionals may have to cope with and treat AMS on their own patients. The medicines and treatment of AMS is presented in Table 2 and 11 (Imray et al 2011, Basnyat and Murdoch 2003, Barry and Pollard 2003, Luks et al 2010).

Mild AMS
Stop, rest and acclimatize 1-2 days, consider descent
Painkiller medicine (Paracetamol, Ibuprofen)
Antiemetics may be useful (metoclopramide)
Acetazolamide if needed
Severe AMS and/or HACE
Descent, oxygen, evacuation
Dexamethasone
Pressure bag if immediately descent is not possible
HAPE
Descent, oxygen, evacuation
Nifedipine
Pressure bag if immediately descent is not possible
Severe AMS that cannot type for HAPE or HACE
Descent, oxygen, evacuation
Dexamethasone
Nifedipine
Pressure bag if immediately descent is not possible

AMS – acute mountain sickness; HACE – high altitude cerebral edema; HAPE – high altitude pulmonary edema

Table 11. Treatment of altitude illness (Barry and Pollard 2003, Luks et al. 2010).

When climbing to altitudes over 3000 meters, the current recommendations are to ascend only 300-600 m per day and to have an acclimatization day for every 600-1200 m of altitude gained (Imray et al. 2011, Basnyat and Murdoch 2003) so that the body can adapt to the altitude. In practice, travellers and climbers usually ascend considerably faster than the recommendation (Karinen et al. 2005). The slight symptoms of AMS may become more serious if the symptoms and warning signs are ignored. Continuing the ascent may lead to HAPE or HACE, which are life threatening conditions. There have been HAPE cases at 1400-2400 m even though these problems are usually found at altitudes over 2500 meters (Gabry et al. 2003, Luks et al 2010). The symptoms may increase in a few hours and the patient may no longer be capable of descent by himself.

During the ascent, one of the most important actions to avoid mountain sickness is sufficient food and drink (Butterfield et al. 1992). Lack of oxygen causes hyperventilation, thus dehydration while breathing increases (Milledge 1992). The adequate amount of fluid at high altitude is not exact but 5-7 litres of fluids per day are usually consumed. Often the trip is made in a different hygiene environment from the travellers' country of origin and diarrhoea and vomiting may disturb the fluid and energy balance of the body (Milledge 1992). Lack of oxygen makes logical thinking more difficult, which may predispose one to serious miscalculations (Cauchy et al.

2002). Young healthy males are often at the greatest risk of AMS because they may ascend too fast too high because of their good physical condition. Physically heavy exertions, such as downhill skiing or climbing, are often begun before the body has had time to adapt to the altitude (Milledge et al. 1991). Travelling in groups gives extra security, but in some cases there may be an unwise competitive spirit. In the group, the objective analysis and reporting of the climbers' own feelings may be forgotten and problems can accumulate when continuing upwards. Tight schedules are also dangerous. It would be good to include extra days in the schedules for rest and adaptation.

The denial of symptoms is common. The case studies (IV) are classic cases of delayed diagnosis and mismanagement of altitude illness. Two climbers developed a severe AMS due to too rapid ascent and their denial of the symptoms. In the first case, the climber first showed signs of AMS soon after leaving the 3000 m camp. The patient did not tell anyone about his symptoms and when asked, he denied all symptoms. Finally AMS was diagnosed at 5300 m altitude. Most probably he had got AMS 1-2 days before at 4800 altitude. The evacuation was delayed because of transport problems and finally he was transported two days later by car from 5300 m to 1500 m where the breathing problems resolved quickly but he was unable to continue the expedition. In the second case, the climber hiked with a rucksack after 3 days acclimatization period from 5000 m to 5400 m altitude where the symptoms started and AMS developed quickly. Correct reaction including the medications and discontinuing the ascent helped to reduce and even to prevent the development of serious problems. After two days' rest, all symptoms disappeared, and he continued to the next camp, which was 200 m higher. The ascent went without problems and no further symptoms of AMS or HAPE occurred.

Prevention is the safest and the most efficient method in the care of AMS. The symptoms may not be easily noticed, thus curative measures may be delayed. Remedying the situation requires radical actions such as interrupting the ascent, descending, patient evacuation etc. The opportunities for medical treatment are limited and a portable pressure chamber and administering additional oxygen bring only temporary relief (Barry and Pollard 2003, Luks et al 2010). Realizing the risk of AMS, making realistic and safe ascent plans, the active elicitation of symptoms and timely reaction to them, in other words, discontinuing the ascent or descending helps to reduce and even to prevent the development of serious problems.

Doctors and nurses in health centres, travel clinics and occupational health care clinics may be approached by patients asking advice on how to plan their trips or treat either themselves or a friend at high altitude, or the health care personnel may take part in an expedition to high altitude environment.

5. FUTURE RECOMMENDATIONS

This study found that SpO_2 changes a day, or a camp, before the onset of AMS. It is associated also with subsequent spectral changes in HRV. These provide sensitive parameters that will supplement the clinical estimation whether subjects are acclimatizing well or are at risk to suffer AMS at higher altitudes in the near future. Nevertheless, clinical decisions should not be based on small differences in SpO_2 or HRV values over time or among individuals, but together with clinical status, and data from other measurements like HR and questionnaires like the Lake Louise questionnaire, it may help to make the right decisions in time. So the future recommendations are:

1. Make realistic and safe ascent plans, include in the schedules extra days for rest and adaptation.
2. All trekking agencies that are organising high altitude treks should have an educational program for their guides.
3. In the field, be active and look for symptoms of AMS and react to them in a timely manner.
4. Take R-SpO_2 and Ex-SpO_2 measurements every day to distinguish those who are acclimatizing well and those who may have problems later. Those whose saturation levels are the lowest could be monitored more intensively. Once climbers have been identified as being at risk, they can be advised by the leaders of teams or expeditions to take additional time to acclimatize.
5. Autonomic cardiac response to increasing altitude could be a low-cost non-invasive test to predict impending AMS but the trigger values typical for impending AMS await further studies.

6. LIMITATIONS AND STRENGTHS

The strengths of these studies were that the rate of ascent, altitude of origin, and time of the day of testing could be controlled. In study II and III, in each group every climber also had a similar diet and physical background and they climbed the same route on mountains over a restricted period of time with essentially the same snow and weather conditions. Barometric pressure varied from day to day, but it was stable during individual measurements. The limitations of our study include relatively few data points during varying degrees of acclimatization with different rates of ascent. As subjects having experienced the symptoms of AMS presumably tend to participate in medical studies more eagerly than those without symptoms, this may lead to a slight overestimation of the prevalence of AMS. On the other hand, because no one

wants to be the weakest link in the expedition, there could be a tendency to hide the symptoms of AMS. There may have been some underestimation of symptoms because of group dynamics or the competitive spirit inside the groups. It is also possible to manipulate SpO_2 values by hyperventilation, even though in the present study this potential source of bias was carefully controlled by the researcher. Arterial O_2 and heart rate are related to the degree of acclimatization, which depends on the rate of ascent. Therefore, some variance in SpO_2 measurements could be related to differences in rate of ascent, which is presented in Figure 5. Within the groups, the ascent rate was the same for all subjects. However, the exercise in Study II was not the same for all subjects, since a heart rate of 150 represents a different percentage of the maximum for each individual. In general, the ascent rate was nearly the same between expeditions. The camps were approximately at the same altitudes; three expeditions were using 11 days to reach the altitude of 5000 m and five used 5-7 days for the same altitude. The different latitude between the Kilimanjaro, Himalaya, and Denali may also have some effects on the degree of acclimatization. The limitations of these studies include the relatively small study group at extreme altitude (> 5000 m). The correlations between HRV parameters and AMS are rather weak. Thus, further studies with larger populations are needed to verify the early changes in HRV between subjects with and without AMS and/or other high-altitude illnesses, especially at extreme altitudes, where the consequences of AMS, HACE, and HAPE may dramatic. The length of HRV measurements at high altitude may have been too short to fully observe trends of changes in HRV variables between subjects with and without AMS or to capture other HRV measures that could reflect more severe periodic breathing. The differences in ascent rates, the places studied, and the altitudes studied may in part explain the differences between the different results. Environmental and/or cardiovascular effects of previous exercise may have been factors in the autonomic patterns observed in subjects with AMS in our study. However, subjects with and without AMS were studied under the same field conditions and after similar recovery times as regards ascent. The ascent rates during the expeditions were normal and widely used in the mountains. Therefore, exercise and environmental factors may not explain the differences in autonomic cardiovascular function observed in association with AMS in this study. HRV is also partially influenced by respiratory rate and depth (Task Force 1996, Penttilä et al. 2001). In the HRV frequency spectrum, power in the entire frequency area, not just the HF band, is also decreased if the respiration rate increases (Task Force 1996). Normally respiration rates will increase somewhat at high altitude, but it is unknown whether the respiration rate is higher in subjects with AMS than in subjects with no AMS. In this study, the subjects were breathing spontaneously and some of the subjects may have had breathing rate close to or below 0.15 Hz, being the lowest boundary for the HF band. For this reason, if altitude or AMS changed respiratory HRV, it cannot be exclusively judged by changes in HF or LF/HF. Unfortunately, sea-level

HRV data was not available for all subjects, so whether those climbers whose basic level of HF is higher could acclimatize better than those whose HF level is lower at sea-level could not be estimated.

Periodic breathing has been reported to exist at high altitude mainly during sleep, but also to some extent when awake (Insalaco et al. 1996, Fan et al. 2012). Because breathing frequency was not measured here, it cannot be excluded completely (McMullen et al. 2012). However, the visual analysis of RRI tachograms, AR spectrum, and Poincare plots do not support the existence of periodic breathing during the measurements. The measurement periods were 2 min so it can be assumed that any significant periodic breathing does not impact on this kind of a measurement period.

CONCLUSIONS AND FUTURE PROSPECTS

In conclusion:

1. The incidence of AMS is very high among the trekkers at Mt Kilimanjaro.

2. Subjects susceptible to AMS had lower SpO_2 at rest and especially during exercise before the clinical manifestations of AMS

3. Daily measurements of SpO_2 at rest and during exercise may help to predict the subsequent AMS at higher altitude if ascent continued.

4. Subjects susceptible to AMS had lower HRV before the clinical manifestations of AMS than those who acclimatized well and did not get AMS 2-5 days later if ascent continued.

5. The treatment of AMS in the field is difficult and time consuming and prevention is the safest and the most efficient method in the care of AMS.

Research may involve the identification of markers of susceptibility and incorporation of these markers into mathematical models to predict the likelihood that AMS will develop. Therefore, is a single or two minutes resting measurement reliable enough to provide a true reflection of an individual's SpO_2 or the balance of autonomic nervous system and its reactions for hypoxia and impending AMS? Portable devices are now available that continuously measure SpO_2 for hours or days at a time. Would measurements during periods of sleep, rest, and exercise provide a better reflection of oxygenation and, therefore, predict AMS with greater accuracy? What kind of combination of portable devices and measurements at the field would help the clinicians or leaders of the expeditions to make correct decisions at correct time? Should persons with a low SpO_2 or changes in HRV parameters take an extra rest day? Or could it finally mean that prophylactic drugs like acetazolamide will be targeted toward persons who really need them?

Clearly, there are many questions to address. However, portable pulse oximeters are here to stay and nearly all explorers and climbers are used to handling pulse meters. In the future, the practical applications of the wrist computers and HR monitors will increase and the analysis of HRV will become easier. Therefore, it is important to all those who venture to altitude to try to identify what the role of these devices should be.

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APPENDIX

1. AMS WORKSHEET

Based on the Lake Louise AMS Questionnaire
Name_____ Age _____ Sex_____ Date _____
Treatment:

	Time					
	Altitude					
1. Headache:						
No headache 0						
Mild headache 1						
Moderate headache 2						
Severe, incapacitating 3						
2. GI:						
No GI symptoms 0						
Poor appetite or nausea 1						
Moderate nausea or vomiting 2						
Severe N&V, incapacitating 3						
3. Fatigue/weak:						
Not tired or weak 0						
Mild fatigue/weakness 1						
Moderate fatigue/weakness 2						
Severe F/W, incapacitating 3						
4. Dizzy/lightheaded:						
Not dizzy 0						
Mild dizziness 1						
Moderate dizziness 2						
Severe, incapacitating 3						
5. Difficulty sleeping:						
Slept well as usual 0						
Did not sleep as well as usual 1						
Woke many times, poor night's sleep 2						
Could not sleep at all 3						
6. Change in mental status:						
No change 0						
Lethargy/lassitude 1						
Disoriented/confused 2						
Stupor/semiconsciousness 3						
7. Ataxia (heel to toe walking):						
No ataxia 0						
Maneuvers to maintain balance 1						
Steps off line 2						
Falls down 3						
Can't stand 4						
8. Peripheral oedema:						
No oedema 0						
One location 1						
Two or more locations 2						
Clinical Assessment Score:						
Total Score:						